DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

P950018

Memorandum

Date FEB 29 1996

From Director, Office of Device Evaluation (HFZ-400)
Center for Devices and Radiological Health (CDRH)

Subject Premarket Approval of Infinitech Inc.'s Perfluoron® (purified perfluoro-n-octane liquid)- ACTION

To The Director, CDRH
ORA _____

ISSUE. Publication of a notice announcing approval of the subject PMA.

FACTS. Tab A contains a FEDERAL REGISTER notice announcing:

(1) a premarket approval order for the above referenced medical device (Tab B); and

(2) the availability of a summary of safety and effectiveness data for the device (Tab C).

RECOMMENDATION. I recommend that the notice be signed and published.

Susan Alpert, Ph.D., M.D.

Attachments
Tab A - Notice
Tab B - Order
Tab C - S & E Summary

DECISION

Approved _____ Disapproved _____ Date _____

Prepared by ET Beers, CDRH, HFZ-460, November 8, 1995, 594-1744.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

[DOCKET NO. _____]

INFINITECH INC.; PREMARKET APPROVAL OF PERFLUORON®(PURIFIED PERFLUORO-N-OCTANE LIQUID)

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing its approval of the application by Infinitech Inc., Chesterfield, MO, for premarket approval, under section 515 of the Federal Food, Drug, and Cosmetic Act (the act), of Perfluoron® (purified perfluoro-n-octane liquid). After reviewing the recommendation of the Ophthalmic Devices Panel, FDA's Center for Devices and Radiological Health (CDRH) notified the applicant, by letter on FEB 29 1996 ___, of the approval of the application.

DATE: Petitions for administrative review by (insert date 30 days after date of publication in the FEDERAL REGISTER).

ADDRESS: Written requests for copies of the summary of safety and effectiveness data and petitions for administrative review, to the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 1-23, 12420 Parklawn Drive, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT:

James F. Saviola, O.D., F.A.A.O.

Center for Devices and Radiological Health (HFZ-460)

Food and Drug Administration

9200 Corporate Blvd.

Rockville, MD 20850

301-594-1744.

SUPPLEMENTARY INFORMATION: On April 28, 1995, Infinitech Inc., Chesterfield, MO 63005, submitted to CDRH an application for premarket approval of Perfluoron® (purified perfluoro-n-octane liquid). The device, a perfluorocarbon liquid, is an intraoperative tool indicated for use during vitreoretinal surgery in patients with primary or recurrent retinal detachment which is complicated by penetrating ocular trauma, giant retinal tear(s) or proliferative vitreoretinopathy (PVR).

On October 19, 1995, the Ophthalmic Devices Panel, an FDA advisory panel, reviewed and recommended approval of the application. On FEB 29 1996, CDRH approved the application by a letter to the applicant from the Director of the Office of Device Evaluation, CDRH.

A summary of the safety and effectiveness data on which CDRH based its approval is on file in the Dockets Management Branch (address above) and is available from that office upon written request. Requests should be identified with the name of the device and the docket number found in brackets in the heading of this document.

OPPORTUNITY FOR ADMINISTRATIVE REVIEW

Section 515(d)(3) of the act (21 U.S.C. 360e(d)(3)) authorizes any interested person to petition, under section 515(g) of the act (21 U.S.C. 360e(g)), for administrative review of CDRH's decision to approve this application. A petitioner may request either a formal hearing under part 12 (21 CFR part 12) of FDA's administrative practices and procedures regulations or a review of the application and CDRH's action by an independent advisory committee of experts. A petition is to be in the form of a petition for reconsideration under 10.33(b) (21 CFR 10.33(b)). A petitioner shall identify the form of review requested (hearing or independent advisory committee) and shall submit with the petition supporting data and information showing that there is a genuine and substantial issue of material fact for resolution through administrative review. After reviewing the petition, FDA will decide whether to grant or deny the petition and will publish a notice of its decision in the FEDERAL REGISTER. If FDA grants the petition, the notice will state the issue to be reviewed, the form of the review to be used, the persons who may participate in the review, the time and place where the review will occur, and other details.

Petitioners may, at any time on or before (insert date 30 days after date of publication in the FEDERAL REGISTER), file with the Dockets Management Branch (address above) two copies of each petition and supporting data and information, identified with the name of the device and the docket number found in brackets in the heading of this document. Received petitions may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

This notice is issued under the Federal Food, Drug, and Cosmetic Act (secs. 515(d), 520(h), (21 U.S.C. 360e(d), 360j(h)) and under authority delegated to the Commissioner of Food and Drugs (21 CFR 5.10) and redelegated to the Director, Center for Devices and Radiological Health (21 CFR 5.53).

Dated: _____.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

Mr. L.E. Mosher
Vice.President
Infinitech Inc.
750 Goddard Avenue
Chesterfield, MO 63005

FEB 29 1996

RE: P950018
Perfluoron® (purified perfluoro-n-octane liquid)
Filed: April 28, 1995
Amended: September 5 and November 30, 1995 and February 16, 1996

Dear Mr. Mosher:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your premarket approval application (PMA) for Perfluoron® (purified perfluoro-n-octane liquid). This device, a perfluorocarbon liquid, is an intraoperative tool indicated for use during vitreoretinal surgery in patients with primary or recurrent retinal detachment which is complicated by penetrating ocular trauma, giant retinal tear(s) or proliferative vitreoretinopathy (PVR). We are pleased to inform you that the PMA is approved subject to the conditions described below and in the "Conditions of Approval" (enclosed). You may begin commercial distribution of the device upon receipt of this letter.

The sale, distribution, and use of this device are restricted to prescription use in accordance with 21 CFR 801.109 within the meaning of section 520(e) of the Federal Food, Drug, and Cosmetic Act (the act) under the authority of section 515(d)(1)(B)(ii) of the act. FDA has also determined that to ensure the safe and effective use of the device that the device is further restricted within the meaning of section 520(e) under the authority of section 515(d)(1)(B)(ii) insofar as the sale, distribution, and use must not violate sections 502(q) and (r) of the act.

Expiration dating for this device has been established and approved at one year. This is to advise you that the protocol you used to establish this expiration dating is considered an approved protocol for the purpose of extending the expiration dating as provided by 21 CFR 814.39(a)(8).

CDRH will publish a notice of its decision to approve your PMA in the FEDERAL REGISTER. The notice will state that a summary of the safety and effectiveness data upon which the approval is based is available to the public upon request. Within 30 days of publication of the notice of approval in the FEDERAL REGISTER, any interested person may seek review of this decision by requesting an opportunity for administrative review, either through a hearing or review by an independent advisory committee, under section 515(g) of the Federal Food, Drug, and Cosmetic Act (the act).

Failure to comply with the conditions of approval invalidates this approval order. Commercial distribution of a device that is not in compliance with these conditions is a violation of the act.

You are reminded that as soon as possible, and before commercial distribution of your device, you must submit an amendment to this PMA submission with copies of all approved labeling in final printed form.

All required documents should be submitted in triplicate, unless otherwise specified, to the address below and should reference the above PMA number to facilitate processing.

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Blvd.
Rockville, Maryland 20850

If you have any questions concerning this approval order, please contact Everette T. Beers, Ph.D. or James F. Saviola, O.D. at (301) 594-1744.

Sincerely yours,

Susan Alpert, Ph.D., M.D.
Director
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

ENCLOSURE

Issued: 5-2-95

CONDITIONS OF APPROVAL

APPROVED LABELING. As soon as possible, and before commercial distribution of your device, submit three copies of an amendment to this PMA submission with copies of all approved labeling in final printed form to the PMA Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration (FDA), 9200 Corporate Blvd., Rockville, Maryland 20850.

ADVERTISEMENT. No advertisement or other descriptive printed material issued by the applicant or private label distributor with respect to this device shall recommend or imply that the device may be used for any use that is not included in the FDA approved labeling for the device. If the FDA approval order has restricted the sale, distribution and use of the device to prescription use in accordance with 21 CFR 801.109 and specified that this restriction is being imposed in accordance with the provisions of section 520(e) of the act under the authority of section 515(d)(1)(B)(ii) of the act, all advertisements and other descriptive printed material issued by the applicant or distributor with respect to the device shall include a brief statement of the intended uses of the device and relevant warnings, precautions, side effects and contraindications.

PREMARKET APPROVAL APPLICATION (PMA) SUPPLEMENT. Before making any change affecting the safety or effectiveness of the device, submit a PMA supplement for review and approval by FDA unless the change is of a type for which a "Special PMA Supplement-Changes Being Effected" is permitted under 21 CFR 814.39(d) or an alternate submission is permitted in accordance with 21 CFR 814.39(e). A PMA supplement or alternate submission shall comply with applicable requirements under 21 CFR 814.39 of the final rule for Premarket Approval of Medical Devices.

All situations which require a PMA supplement cannot be briefly summarized, please consult the PMA regulation for further guidance. The guidance provided below is only for several key instances.

A PMA supplement must be submitted when unanticipated adverse effects, increases in the incidence of anticipated adverse effects, or device failures necessitate a labeling, manufacturing, or device modification.

A PMA supplement must be submitted if the device is to be modified and the modified device should be subjected to animal or laboratory or clinical testing designed to determine if the modified device remains safe and effective.

A "Special PMA Supplement - Changes Being Effected" is limited to the labeling, quality control and manufacturing process changes specified under 21 CFR 814.39(d)(2). It allows for the **addition** of, but **not the replacement** of previously approved, quality control specifications and test methods. These changes may be implemented before FDA approval upon acknowledgment by FDA that the submission is being processed as a "Special PMA Supplement - Changes Being Effected." This acknowledgment is in addition to that issued by the PMA Document Mail Center for all PMA supplements submitted. **This procedure is not applicable to changes in device design, composition, specifications, circuitry, software or energy source.**

Alternate submissions permitted under 21 CFR 814.39(e) apply to changes that otherwise require approval of a PMA supplement before implementation of the change and include the use of a 30-day PMA supplement or annual postapproval report. FDA must have previously indicated in an advisory opinion to the affected industry or in correspondence with the applicant that the alternate submission is permitted for the change. Before such can occur, FDA and the PMA applicant(s) involved must agree upon any needed testing protocol, test results, reporting format, information to be reported, and the alternate submission to be used.

POSTAPPROVAL REPORTS. Continued approval of this PMA is contingent upon the submission of postapproval reports required under 21 CFR 814.84 at intervals of 1 year from the date of approval of the original PMA. Postapproval reports for supplements approved under the original PMA, if applicable, are to be included in the next and subsequent annual reports for the original PMA unless specified otherwise in the approval order for the PMA supplement. Two copies identified as "Annual Report" and bearing the applicable PMA reference number are to be submitted to the PMA Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration, 9200 Corporate Blvd., Rockville, Maryland 20850. The postapproval report shall indicate the beginning and ending date of the period covered by the report and shall include the following information required by 21 CFR 814.84:

(1) Identification of changes described in 21 CFR 814.39(a) and changes required to be reported to FDA under 21 CFR 814.39(b).

(2) Bibliography and summary of the following information not previously submitted as part of the PMA and that is known to or reasonably should be known to the applicant:

(a) unpublished reports of data from any clinical investigations or nonclinical laboratory studies involving the device or related devices ("related" devices include devices which are the same or substantially similar to the applicant's device); and

(b) reports in the scientific literature concerning the device.

If, after reviewing the bibliography and summary, FDA concludes that agency review of one or more of the above reports is required, the applicant shall submit two copies of each identified report when so notified by FDA.

ADVERSE REACTION AND DEVICE DEFECT REPORTING. As provided by 21 CFR 814.82(a)(9), FDA has determined that in order to provide continued reasonable assurance of the safety and effectiveness of the device, the applicant shall submit 3 copies of a written report identified, as applicable, as an "Adverse Reaction Report" or "Device Defect Report" to the PMA Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration, 9200 Corporate Blvd., Rockville, Maryland 20850 within 10 days after the applicant receives or has knowledge of information concerning:

(1) A mixup of the device or its labeling with another article.

(2) Any adverse reaction, side effect, injury, toxicity, or sensitivity reaction that is attributable to the device and

(a) has not been addressed by the device's labeling or

(b) has been addressed by the device's labeling, but is occurring with unexpected severity or frequency.

(3) Any significant chemical, physical or other change or deterioration in the device or any failure of the device to meet the specifications established in the approved PMA that could not cause or contribute to death or serious injury but are not correctable by adjustments or other maintenance procedures described in the approved labeling. The report shall include a discussion of the applicant's assessment of the change, deterioration or failure and any proposed or implemented corrective action by the applicant. When such events are correctable by adjustments or other maintenance procedures described in the approved labeling, all such events known to the applicant shall be included in the Annual Report described under "Postapproval Reports" above unless specified otherwise in the conditions of approval to this PMA. This postapproval report shall appropriately categorize these events and include the number of reported and otherwise known instances of each category during the reporting period. Additional information regarding the events discussed above shall be submitted by the applicant when determined by FDA to be necessary to provide continued reasonable assurance of the safety and effectiveness of the device for its intended use.

REPORTING UNDER THE MEDICAL DEVICE REPORTING (MDR) REGULATION. The Medical Device Reporting (MDR) Regulation became effective on December 13, 1984, and requires that all manufacturers and importers of medical devices, including in vitro diagnostic devices, report to FDA whenever they receive or otherwise became aware of information that reasonably suggests that one of its marketed devices

(1) may have caused or contributed to a death or serious injury or

(2) has malfunctioned and that the device or any other device marketed by the manufacturer or importer would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

The same events subject to reporting under the MDR Regulation may also be subject to the above "Adverse Reaction and Device Defect Reporting" requirements in the "Conditions of Approval" for this PMA. FDA has determined that such duplicative reporting is unnecessary. Whenever an event involving a device is subject to reporting under both the MDR Regulation and the "Conditions of Approval" for this PMA, you shall submit the appropriate reports required by the MDR Regulation and identified with the PMA reference number to the following office:

Division of Surveillance Systems (HFZ-531)
Center for Devices and Radiological Health
Food and Drug Administration
1350 Piccard Drive, Room 240
Rockville, Maryland 20850
Telephone (301) 594-2735

Events included in periodic reports to the PMA that have also been reported under the MDR Regulation must be so identified in the periodic report to the PMA to prevent duplicative entry into FDA information systems.

Copies of the MDR Regulation and an FDA publication entitled, "An Overview of the Medical Device Reporting Regulation," are available by written request to the address below or by telephoning 1-800-638-2041.

Division of Small Manufacturers Assistance (HFZ-220)
Center for Devices and Radiological Health
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. GENERAL INFORMATION

A. Device Generic Name: Perfluorocarbon Liquid (ProCode LWL - Intraocular Fluid)
B. Device Trade Name: PERFLUORON®[1] (purified perfluoro-n-octane liquid)
C. Applicant's Name and Address:

INFINITECH™, INCORPORATED
750 Goddard Avenue
Chesterfield, Missouri 63005

D. Investigational Device Exemption (IDE) Number: G900249
E. Date of Panel Recommendation: October 19, 1995
F. Premarket Approval Application: P950018
Date Filed: April 28, 1995
G. GMP Inspection: November 8, 1995
H. Date of Notice of Approval to Applicant: FEB 29 1996

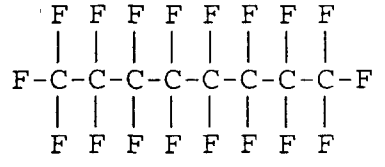
II. INDICATIONS FOR USE

PERFLUORON is an intraoperative tool indicated for use during vitreoretinal surgery in patients with primary or recurrent retinal detachment which is complicated by penetrating ocular trauma, giant retinal tear(s) or proliferative vitreoretinopathy (PVR).

III. DEVICE DESCRIPTION

PERFLUORON (purified perfluoro-n-octane liquid) is sterile, non-pyrogenic, purified perfluoro-n-octane (≥ 99.9% PFNO) for temporary use as a mechanical tool during vitreoretinal surgery. Perfluoro-n-octane is a member of the perfluorocarbon chemical family, a family of chemicals composed of carbon and fluorine atoms. Perfluorocarbons exhibit high oxygen solubility and are relatively inert substances with little biological toxicity potential.

The structure of the molecule is:



C_8F_{18}, or $CF_3(CF_2)_6CF_3$
(CAS No. 307-34-6)

[1] PERFLUORON is a registered trademark of Infinitech, Inc.

PERFLUORON is optically clear, has a high vapor pressure and low viscosity, and, compared to aqueous, has a lower refractive index and a much higher specific gravity. It is inert and immiscible in water, ionic solutions and common organic chemicals.

The chemical and physical properties of PERFLUORON are listed below.

Molecular Weight	438
Boiling Point (°C @ 760 mmHg)	105-105.5
Specific Gravity (g/cc @ 25°C)	1.754
Surface Tension (dynes/cm, 27.2°C)	16.98
Refractive Index	1.27
Vapor Pressure (mmHg. @ 37°C)	52
Viscosity (centistoke @ 25°C)	0.69

PERFLUORON has the following chemical and physical specifications:

Purity (%, v/v)	≥ 99.9
Reactive Fluoride (μg/ml)	< 3
Non-volatile Residue (μg/ml)	≤ 20
Heavy Metals (ppm)	≤ 10
Particulates	Not more than 50 particles/ml ≥ 10 μm Not more than 5 particles/ml ≥ 25 μm
Hydrogen Ion Content (ppm, w/w)	< 1

PERFLUORON contains no preservatives or other ingredients.

PERFLUORON is supplied in a kit containing a 5 ml. vial of PERFLUORON, together with a) one Millipore Millex-FG, 0.2 μm microbial filter unit, b) one B-D 10 cc syringe, c) one 20 gauge x 1½", beveled needle, and d) one 23 gauge blunt cannula. All components are sterile in individual sterile packages, but the lidded tray is *not sterile*.

IV. CONTRAINDICATIONS, WARNINGS, AND PRECAUTIONS

A. Contraindications

- PERFLUORON is contraindicated for long-term use in the eye or as a vitreous replacement.

B. Warnings

- PERFLUORON should not be injected directly into the vitreous, or injected simultaneously with aspiration of the vitreous, as severe intraocular damage may occur.

- At the conclusion of the surgical procedure, PERFLUORON must be completely removed from the eye, and be replaced with an appropriate vitreous substitute.

C. Precautions

- Directions for Use of PERFLUORON should be followed closely.

- Subretinal migration, or placement, of PERFLUORON may occur during the injection of the device. (See Directions for Use)

- The safety and effectiveness of the use of PERFLUORON in patients under 15 months of age has not been established.

- During the clinical trials, posterior retinal slippage occurred at the anterior edge of the giant retinal tear in 18% of patients with Giant Retinal Tears. (See Directions for Use)

- To avoid inadvertent placement of PERFLUORON behind the retina during injection, the final fill level in the eye should always remain posterior to any large retinal breaks.

- If PERFLUORON is introduced into a large retinal break, it may slip into the subretinal space. Special care should be taken to examine for and remove any subretinal PERFLUORON through an existing posterior tear or through a posterior retinotomy prior to the completion of surgery. (See Directions for Use)

- Do not resterilize PERFLUORON.

- Do not admix PERFLUORON with any other substances prior to use.

- Do not use PERFLUORON after its expiration date.

V. ALTERNATIVE PRACTICES OR PROCEDURES

The management of complicated retinal detachment associated with giant retinal tears has stimulated the development of many approaches to unfold the flap of the tear and maintain its position against the retinal pigment epithelium. The use of intraocular gases may necessitate turning the patient intraoperatively into the prone position to help unroll the flap of the tear. Surgical tables have been designed for this purpose.

Silicone oil techniques involve direct bimanual manipulation of the retina under the silicone oil interface until the flap is correctly positioned. A posterior retinotomy is occasionally necessary to evacuate residual subretinal fluid after the tear is closed.

Methods have also been developed to fixate the flap of the tear intraoperatively, such as retinal incarceration or microincarceration retinal suturing or retinal tacks.

Various liquid devices with a higher specific gravity than water have also been used to unfold the flap of a giant retinal tear, and to flatten the retina against the choroidal surface. The use of hyaluronate sodium or silicone oil has been previously reported, but only in a few patients.

VI. MARKETING HISTORY

PERFLUORON has not been marketed in the United States or any foreign country.

VII. ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Adverse Events reported during the clinical trial of PERFLUORON include enucleation (3 eyes, 1 day to 1 month following surgery), heart attack (1 patient, 8 days following surgery) and death (1 patient, greater than 3 months after surgery). None were considered to be associated with the use of PERFLUORON. These rates of complication may be influenced by the duration of follow-up.

The following adverse reactions related to the use of PERFLUORON were observed during the clinical trials:

- Intraoperative Subretinal PERFLUORON Migration 8.1%
- Postoperative Residual PERFLUORON 6.3%

Other complications reported by the investigators are general complications of complicated vitreoretinal surgery, and were not associated specifically to the use of PERFLUORON:

- Corneal abnormalities 46%
- Anterior Chamber Abnormalities 34%
- Elevated IOP 18%
- Hypotony 15%
- Iris Abnormalities 15%
- Cataract Formation in phakic eyes 13.8%
- Intraoperative Retinal Slippage 8.4%
- Progression to NLP (No Light Perception) 4.4%

VIII. DOSAGE AND ADMINISTRATION

A. General

Background

Detachment of the retina is usually spontaneous and may be secondary to trauma. Retinal breaks or tears are the most important predisposing factor. In the presence of a tear or break, fluid from the vitreous cavity percolates through the defect into the subretinal space, and combined with abnormal vitreous traction on the retina and the force of gravity, leads to the detachment.

General Properties

PERFLUORON, by virtue of its high specific gravity, functions as a mechanical tool during vitreoretinal surgery, providing hydrokinetic manipulation of the detached retina. This high specific gravity allows PERFLUORON to be infused over the posterior portion of the retina and facilitates retinal flattening and anterior displacement of subretinal fluid.

PERFLUORON has a significantly different refractive index than Aqueous (1.27 vs 1.33) which assists intraocular visualization and control of the device. It is optically clear, and does not interfere with visualization of the retina.

PERFLUORON is immiscible with water, ionic solutions, and common organic chemicals. It tends to form into droplets, rather than dispersing. These physical properties make it easy to observe during surgery, and to remove by aspiration at the conclusion of the intraoperative procedure.

PERFLUORON has a high vapor pressure which facilitates removal of residual material remaining after aspiration. At room temperature, during the fluid-gas exchange procedure at the conclusion of surgery, any remaining portion of the device will usually evaporate and exit through the sclerotomy sites.

General Use

PERFLUORON should be slowly injected over the optic disc to flatten the retina posteriorly. As the retina is flattened, examine it for areas of residual membranes, for traction remaining on the retina and for the presence of previously undetected posterior breaks. Such membranes should be removed or peeled to the extent possible. If large posterior breaks are detected, additional application of PERFLUORON should be discontinued. If no large posterior breaks are present, PERFLUORON should be infused up to the level of the most posterior retinal break, forming a "bubble" in the posterior portion of the retina.

The weight of PERFLUORON on the posterior retina displaces subretinal fluids anteriorly, resulting in a flattened retina up to the edge of the most posterior break. Membrane removal, if necessary, is performed in the aqueous phase with PERFLUORON providing

mechanical stabilization of the posterior retina. Areas of residual traction which cannot be freed by dissection may be subject to retinotomy anterior to the bubble. Thermal adhesive treatment can be applied to the edges of the flattened retina through the bubble. If the edge of the tear is too peripheral for endophotocoagulation, transcleral cryotherapy can be applied.

Air-fluid exchange is then performed. With the use of a flute needle, infusion fluid above the bubble should be removed as completely as possible by using air to flatten the anterior retina and displace all anterior subretinal fluid before removal of the PERFLUORON. Endophotocoagulation to the anterior retina should be applied, as indicated.

If PERFLUORON is introduced into a large retinal break, it may slip behind the retinal detachment. This event can be handled by the complete aspiration of the device with either a 20 or 23 gauge cannula, utilizing the break through which it originally migrated. If aspiration at the primary break site does not provide complete removal, a retinotomy should be performed to remove all PERFLUORON.

Occasionally, PERFLUORON may be inadvertently dispersed during injection, resulting in small bubbles (droplets) that are not identified and completely aspirated at the conclusion of surgery. Dispersion of the PERFLUORON can be best controlled by keeping the 23 gauge blunt cannula recommended for injection in the middle of the PERFLUORON bubble as more of the device is injected, and away from the tip of any active infusion cannula.

During the clinical trials, residual droplets of PERFLUORON were occasionally observed in either the anterior or posterior chamber postoperatively. These droplets were not associated with any adverse reactions or complications, but if the situation does arise, it may be necessary to remove the residual PERFLUORON by surgery.

B. In GIANT RETINAL TEARS[1]

PERFLUORON should be injected with the patient in the supine position to gently unfold the flap of the tear, and to flatten the retina against the choroidal surface.

If epiretinal membranes are present, they should be removed from both surfaces of the retina, as completely as possible, by conventional means. A small amount of PERFLUORON (0.8 to 1.0 ml) should then be injected over the optic disc. As any additional epiretinal membranes are exposed and removed, more PERFLUORON can be slowly injected up to the edge of the tear.

Once the retina is unfolded and the tear is positioned, an appropriate thermal adhesive modality should be applied, through the PERFLUORON, along the edge of the tear. A scleral buckle may be placed before the PERFLUORON is removed.

Remove the PERFLUORON at the conclusion of the procedure by aspiration through either a 23-gauge or flute needle during the air/fluid exchange.

During the clinical trials, posterior retinal slippage occurred at the equator of the giant retinal tear in 18% of patients with Giant Retinal Tears. To reduce the potential for the edge of the flap to move posteriorly, carefully remove all saline at the edge of the break before proceeding with the aspiration of PERFLUORON posteriorly. This maneuver reduces the chance of slippage by removing subretinal fluids that might otherwise tend to flow posteriorly. Retinal slippage, if it occurs during the fluid-air exchange, can be corrected by replacing some of the air with saline solution and by using an expanding gas concentration after turning the patient into the appropriate position postoperatively.

When gas tamponade is chosen, an automated air infusion system should be used during fluid-air exchange. A flute or extrusion needle with a soft silicone tip may be used, being placed first near the margin of the tear. As the gas bubble descends, it flattens the anterior retina, expressing the subretinal fluid through the break. All saline at the edge of the break should be carefully removed before proceeding to aspirate the PERFLUORON posteriorly. This maneuver reduces the chance of slippage of the posterior flap.

The intrinsic elasticity of the detached retina may result in extensive slipping and retinal folding under air. When this occurs, the air should be replaced by balanced saline, and the PERFLUORON re-injected to reposition the retinal detachment. When the tear is repositioned, direct exchange of PERFLUORON for silicone oil, which engages the edge of the tear as it descends, will prevent slippage and folding of the retina.

When silicone oil is selected for extended tamponade, the PERFLUORON may be directly aspirated as the silicone oil is injected with an automated infusion pump. When the silicone oil is first injected, a soft-tipped flute or extrusion needle is placed anteriorly near the edge of the tear to aspirate all saline anterior to the PERFLUORON. When the silicone bubble contacts the PERFLUORON, the interface is visible and the PERFLUORON is aspirated in an anterior-to-posterior direction.[2]

When silicone oil is selected for extended retinal tamponade, small droplets of PERFLUORON may be difficult to distinguish from air bubbles that have become mixed with the silicone oil during its infusion. However, within seconds, air bubbles will float anteriorly in the silicone oil, while the small PERFLUORON droplets will descend onto the surface of the retina, making them easier to identify and aspirate. [2]

C. In PROLIFERATIVE VITREORETINOPATHY (PVR)[3]

PERFLUORON is a useful intraoperative instrument for the hydrokinetic manipulation of the retina during vitrectomy surgery for proliferative vitreoretinopathy. PERFLUORON permits manipulation of the retina with the patient in the supine position.

After epiretinal membrane dissection and removal of all visible posterior preretinal membranes, inject the PERFLUORON into the funnel of the retinal detachment, positioned directly above the optic disc. Areas of residual traction and membranes may be exposed as the PERFLUORON fills the posterior chamber. The PERFLUORON interface should be kept posterior to these areas, and epiretinal membranes removed in a posterior to

anterior direction. More PERFLUORON may be injected as needed, up to the level of the most posterior retinal break.

D. In OCULAR TRAUMA[4]

Penetrating ocular trauma elicits a broad range of ocular responses, including intraocular bleeding, severe inflammation, fibrous proliferation, scarring, and cyclitic membrane formation. Retinal detachment may result from these processes or from the injury itself.

PERFLUORON is a useful intraoperative tool during such vitreoretinal surgery in the repair of severe ocular trauma, using the techniques described previously for hydrokinetic manipulation of the retina.

E. Post-Procedure

PERFLUORON **must be removed** at the conclusion of the procedure by aspiration through either a 23-gauge or flute needle during the air/fluid exchange (see WARNINGS).

VIII. SUMMARY OF STUDIES

A. Non-clinical Studies

1. Safety and Toxicity Studies

A series of non-clinical studies were undertaken to demonstrate that PERFLUORON used intraoperatively in retinal detachment surgery and removed immediately after the surgery, could reasonably be expected to be non-toxic and raise no safety concerns. A complete list of all non-clinical testing on this material is presented below.

IN VITRO TESTS

Cytotoxicity: Material extracted in MEM and exposed to mouse fibroblast cells for up to 72 hrs.	non-toxic
Cell Growth Inhibition (1-pt): Material extracted in distilled water and exposed to mouse fibroblast cells for up to 72 hrs, then assayed for protein content and cell inhibition.	non-toxic
Hemolysis: Material placed in direct contact with rabbit blood/saline mix for one hour.	non-hemolytic
Ames Mutagenicity: Standard Ames test using a saline extract and tester strains TA98, TA100, TA1535, TA1537, and TA1538.	non-mutagenic
LAL-Pyrogen: Standard test using E. coli; product diluted 1:8 in LAL-Reagent Water.	< 0.25 EU/ml

Fibroblast Behavior: From: Sparrow et al., *Fibroblast behavior of aqueous interfaces with perfluorocarbon, silicone, and fluorosilicone liquids*, Invest. Ophthal. & Vis. Sci., 31:4, 638-646, 1990. Material in direct contact with fibroblasts cultured from the thigh of a rabbit. In this test, minimum cell growth is indicative of the relative biological inertness of the material. — minimum cell growth

IN VIVO TESTS

Acute Systemic Toxicity: USP <661> using saline (SC) and cotton seed oil (CSO) extracts in mice, observed for 72 hrs. — non-toxic

Intracutaneous Toxicity: USP <661> using saline (SC) and cotton seed oil (CSO) extracts in rabbits, observed for 72 hrs. — non-toxic

Guinea Pig Maximization: Standard dermal sensitization in the guinea pig using SC and CSO extracts of the material. — non-sensitizer

Intraocular Irritation: Material injected into the anterior chamber of one eye of rabbits; examined after 3 days; no evidence of corneal or intraocular toxicity. — non-irritant

Intravitreal Injection: Six rabbits were anesthetized, then 0.2 ml of the vitreous was removed and replaced with either the test material or balanced saline. The eyes were examined for 48 hrs for evidence of irritation. — non-irritant

Retinal & Intraocular Tolerance: From: Chang, et al., *Experimental studies of tolerance to intravitreal perfluoro-n-octane liquid*, Retina, 11:4, pp 367-374, 1991. Vitrectomized rabbits and vitrectomized pigs were injected with perfluoro-n-octane (PFnO) with observation periods ranging from 48 hrs to 6 months.

Short term exposure (up to 1 week) (rabbit, pig)	Well-tolerated
Extended exposure to residual PFnO (0.1 ml) (up to 6 mon)	Well-tolerated
Extended term exposure (1 wk to 6 mon) (rabbit)	**Poorly-tolerated**

2. Sterilization. PERFLUORON contains no preservatives or other ingredients. PERFLUORON is supplied in a kit containing a 5 ml. vial of PERFLUORON, together with a) one Millipore Millex-FG, 0.2 µm microbial filter unit, b) one B-D 10 cc syringe, c) one 20 gauge x 1½", beveled needle, and d) one 23 gauge blunt cannula. All components are sterile in individual sterile packages, but the lidded tray is *not sterile*. Sterilization of the vial of PERFLUORON is achieved by aseptic fill.

3. Shelf-Life Dating. Shelf life testing results support a one year shelf life. A shelf life and stability protocol is approved.

B. Clinical Studies

The data upon which the claims of safety and effectiveness for Infinitech's PERFLUORON are based were derived from twenty centers in the U.S. in a prospective clinical trial. In that trial, 395 PERFLUORON-assisted surgeries were conducted at 20 participating centers from April 20, 1992 through October 24, 1994. Historical control data were collected from 123 patients at four of the centers participating in the trial. Control ("CTRL") procedures were selected from sequential cases performed from January 1989 through February 1990. Later data were not reliable as a control due to the gradually increasing availability and use of various unapproved liquid perfluorocarbon devices beginning in early 1990.

1. Subject Selection and Exclusion Criteria

To be included in the investigation, subjects had to meet all of the following inclusion and exclusion criteria:

Inclusion Criteria
Complicated retinal detachment involving proliferative vitreoretinopathy, giant tear, and/or penetrating traumatic injury, and
Adults and children (at least 15 months old), and
Able to comply with postoperative follow-up requirements, and
Able to provide informed consent.

Exclusion Criteria
Retinal detachments other than those described above, or
Children under the age of 15 months, or
Unable to comply with postoperative follow-up requirements, or
Unable to provide informed consent, or
Intraoperative discovery of posterior retinal breaks which could allow the Device to enter the subretinal space.

2. Data Presentation: Core Group and Supplemental Group

For purposes of statistical analyses, PERFLUORON-assisted procedures were stratified into two groups: 1) a "Core" group consisting of patients entered into the study on or before April 13, 1994, and 2) a "Supplemental" group consisting of patients entered into the study from April 14, 1994 through October 24, 1994. All control procedures were performed from January 1989 through February 1990 and were classified as "Core" group patients.

3. Study Population

Infinitech's clinical investigation of PERFLUORON involved subjects with seriously diseased eyes having complicated retinal detachments. Specific clinical presentations included retinal detachment due to proliferative vitreoretinopathy ("PVR"), giant retinal

tears ("GRT"s) and retinal detachments due to trauma.

"PVR" was operationally defined as any retinal detachment due to proliferative vitreoretinopathy in the absence of GRT or trauma. "GRT" was defined as giant retinal tear not associated with trauma. PVR may or may not have been present. "TRAUMA" was defined as any retinal detachment in the presence of ocular trauma. PVR and/or GRT may have been present. Any case not classified as PVR, GRT or trauma was designated as "OTHER". Other retinal detachments typically presented with ocular hemorrhage of a non-traumatic origin in the absence of PVR and GRT.

The study population included 395 PERFLUORON-assisted surgeries conducted from April 20, 1992 through October 24, 1994 and 123 historical control procedures ("CTRL") selected from sequential cases performed from January 1989 through February 1990.

Number of Patients per Center				
Center Code	Center Name	PERFLUORON Core Group[2]	PERFLUORON Supplemental Group[3]	Control Group
UCLA	Jules Stein UCLA	17	5	8
PENN	Penn State University	4	-	-
DALL	Dallas Presbyterian	14	13	39
STJO	Retina Center at St. Joseph's	44	14	-
PAC	Pacific Medical Center	1	-	-
STLUK	St. Lukes	1	2	-
ASSOC	Assoc. Retinal Consultants	33	7	-
BPEI	Bascom Palmer Eye Institute	26	12	-
DUKE	Duke Eye Center	13	15	50
EMORY	Emory University	9	11	-
MASS	Mass. Eye & Ear Infirmary	14	3	-
WISC	Medical College of Wisconsin	25	7	26
STAN	Stanford Medical Center	17	4	-
CLEV	The Cleveland Clinic	4	12	-
TUL	Tulane Medical Center	1	5	-
OREG	Oregon Health Sciences Foundation	-	5	-
BAY	Methodist Hospital, Baylor	-	31	-
MCGEE	Dean McGee Eye Center	2	18	-

Number of Patients per Center				
Center Code	Center Name	PERFLUORON Core Group[2]	PERFLUORON Supplemental Group[3]	Control Group
INGAL	Ingalls Memorial	-	1	-
SOUTH	Health South	1	4	-
TOTAL		229	169	123

[1] One patient at UCLA entered the study twice: OS is #022, OD is #381.
[2] All patients treated on or before 4/13/94
[3] All patients treated from 4/14/94 through 10/24/94

4. Pre-procedural (Baseline) Data

a. Clinical Presentation

In the PERFLUORON group, initial clinical presentation included 213 "pure" PVR's, 87 GRT's, 86 detachments secondary to trauma, and 9 "other" detachments. "Other" retinal detachments typically presented with ocular hemorrhage of a non-traumatic origin. The most common presentation in the PERFLUORON group and the control group was PVR (perfluoro-n-octane: 53.9%, CTRL: 52.0%).

Clinical Presentation		
Presentation	PERFLUORON Group	Control Group
PVR	53.9% (213/395)	52.0% (64/123)
GRT	22.0% (87/395)	12.2% (15/123)
TRAUMA	21.8% (86/395)	35.8% (44/123)
OTHER	2.3% (9/395)	-

b. Demographics

Average age at the time of detachment varied according to clinical presentation. Patients presenting with PVR tended to be older than those presenting with GRT. Patients in both of these groups tended to be older than those with detachments resulting from trauma.

Average Age (Std Dev) at Time of Procedure*		
Presentation	PERFLUORON Group	Control Group
PVR	57.3 (19.9)	59.1 (17.5)
GRT	38.6 (19.3)	45.8 (13.8)
TRAUMA	33.1 (18.6)	30.5 (18.2)
OTHER	54.7 (22.1)	-

* DOB not reported for 2 PVR cases, 1 GRT case and 3 trauma cases in the PERFLUORON Group

Overall, approximately 70% (272/395) of the study participants were male. The proportion of males varied somewhat according to clinical presentation.

Prevalence of Male Gender		
Presentation	PERFLUORON Group	Control Group
TOTAL	68.8% (272/395)	69.9% (86/123)
PVR	60.6% (129/213)	59.4% (38/64)
GRT	75.9% (66/87)	80.0% (12/15)
TRAUMA	82.6% (71/86)	81.8% (36/44)
OTHER	66.7% (6/9)	-

In both the PERFLUORON group and the control group, approximately 80% (perfluoro-n-octane: 277/352, CTRL: 78/97) of the study participants were Caucasian and approximately 13% (perfluoro-n-octane: 42/352, CTRL: 14/97) were Black. The remaining participants were Hispanic (perfluoro-n-octane: 8.5% (30/352), CTRL: 4.1% (4/97)) or Asian (perfluoro-n-octane: 1% (3/352), CTRL: 1% (1/97)).

The overall prevalence of diabetes in the PERFLUORON group was 15.7% (54/344) which was higher than the 8.4% (10/119) rate observed among controls. Over 90% (60/64) of the patients with a history of diabetes presented with PVR (n=50) or GRT (n=10).

History of Prior Ocular Surgery*		
Presentation	PERFLUORON Group	Control Group
TOTAL	79.9% (315/394)	78.5% (95/121)
PVR	90.1% (191/212)	95.3% (61/64)
GRT	58.6% (51/87)	71.4% (10/14)
TRAUMA	76.7% (66/86)	55.8% (24/43)
OTHER	77.8% (7/9)	-

* not recorded for 1 PVR patient in the PERFLUORON group; not recorded for 1 Trauma and 1 GRT patient in Control group.

Approximately 80% of both PERFLUORON assisted cases (315/394=80.0%) and controls (95/121=78.5%) had ocular surgery prior to entering the study.

Over 55% of PERFLUORON assisted cases (220/393) had a history of prior retinal detachment in the treated eye, and slightly over 40% (172/394) of treated eyes were previously vitrectomized. Corresponding figures for controls were 63% (75/120, prior detachment) and 52% (63/121, vitrectomy).

History of Prior Retinal Detachment*		
Presentation	PERFLUORON Group	Control Group
TOTAL	55.9% (220/393)	62.5% (75/120)
PVR	72.8% (155/213)	88.9% (56/63)
GRT	30.2% (26/86)	50.0% (7/14)
TRAUMA	42.4% (36/85)	27.9% (12/43)
OTHER	33.3% (3/9)	-

* not recorded for 1 GRT and 1 Trauma in the PERFLUORON group; not recorded for 1 PVR, 1 Trauma and 1 GRT patient in CONTROL group.

History of Prior Vitrectomy*		
Presentation	PERFLUORON Group	Control Group
TOTAL	43.7% (173/394)	52.0% (63/121)
PVR	53.3% (113/212)	68.8% (44/64)
GRT	27.6% (24/87)	42.9% (6/14)
TRAUMA	38.4% (33/86)	30.2% (13/43)
OTHER	22.2% (2/9)	-

* not recorded for 1 PVR patient in the PERFLUORON group; not recorded for 1 Trauma and 1 GRT patient in the CONTROL group.

Eighty-five percent of the eyes in the PERFLUORON assisted group (309/362) and 81% (84/104) of the controls had normal intraocular pressures (IOP's) prior to their procedures. The majority of abnormal IOP's in both groups were below normal (hypotony). In the PERFLUORON-assisted abnormal IOP group, the incidence of hypotony was 45/53 (85%), and in the control group it occurred in 95% (19/29) of the subjects. Hypotony was operationally defined as any value below 5mm Hg. Elevated IOP was defined as any value above 30 mmHg.

Twenty-two percent of eyes in the PERFLUORON assisted group (87/392) and 26% (32/121) of the controls were phakic. The prevalence of pseudophakic eyes, aphakic eyes and cataracts differed by clinical presentation.

Lens Status at Presentation (PERFLUORON- assisted group)*				
Presentation	Phakic	Pseudophakic	Aphakic	Cataract
TOTAL	22.2% (87/392)	30.1% (118/392)	26.3% (103/392)	21.4% (84/392)
PVR	10.8% (23/213)	44.6% (95/213)	19.3% (41/213)	25.4% (54/213)
GRT	41.2% (35/85)	17.7% (15/85)	21.2% (18/85)	20.0% (17/85)
TRAUMA	29.4% (25/85)	7.1% (6/85)	49.4% (42/85)	14.1% (12/85)
OTHER	44.4% (4/9)	22.2% (2/9)	22.2% (2/9)	11.1% (1/9)

* not recorded for 1 TRAUMA case and 2 GRT cases in the PERFLUORON assisted group

Lens Status at Presentation (Control group)*				
Presentation	Phakic	Pseudophakic	Aphakic	Cataract
TOTAL	26.4% (32/121)	24.5% (30/121)	25.6% (31/121)	23.1% (28/121)
PVR	12.7% (8/63)	36.5% (23/63)	19.1% (12/63)	31.8% (20/63)
GRT	33.3% (5/15)	26.7% (4/15)	20.0% (3/15)	20.0% (3/15)
TRAUMA	44.2% (19/43)	7.0% (3/43)	37.2% (16/43)	11.6% (5/43)

* not recorded for 1 TRAUMA case and 1 PVR case in the control group

Approximately 17% of eyes in the PERFLUORON assisted group (65/388) and 8% of the controls (9/116) had minimum functional vision. Minimum functional vision was defined as visual acuity equal to 20/400 or better.

Visual Acuity at Presentation (PERFLUORON assisted group)*				
Presentation	Min.Functional	20/401 to Count Fingers (CF)	Hand Motion (HM)	Light Perception (LP)
TOTAL	16.8% (65/388)	22.4% (87/388)	34.0% (132/388)	26.3% (102/388)
PVR	11.0% (23/209)	23.9% (49/209)	42.6% (89/209)	22.5% (47/209)
GRT	37.7% (32/85)	23.5% (21/85)	20.0% (17/85)	18.8% (16/85)
TRAUMA	8.2% (7/83)	20.0% (17/83)	29.4% (25/83)	40.0% (34/83)
OTHER	33.3% (3/9)	0.0% (0/9)	11.1% (1/9)	55.6% (5/9)

* not recorded for 1 TRAUMA case, 2 GRT cases and 5 PVR in the PERFLUORON assisted group. NLP for 2 TRAUMA cases.

Visual Acuity at Presentation (Control group)*				
Presentation	Min.Functional	20/401 to Count Fingers (CF)	Hand Motion (HM)	Light Perception (LP)
TOTAL	7.8% (9/116)	12.1% (14/116)	43.1% (50/116)	36.2% (42/116)
PVR	6.4% (4/63)	6.4% (4/63)	50.8% (32/63)	36.5% (23/63)
GRT	30.8% (4/13)	23.1% (3/13)	30.8% (4/13)	15.4% (2/13)
TRAUMA	2.5% (1/39)	17.5% (7/39)	35.0% (14/39)	42.5% (17/39)

* not recorded for 4 TRAUMA cases, 2 GRT cases and 1 PVR case in the control group. NLP for 1 trauma case.

5. Procedural Data

a. Acute Anatomical Success

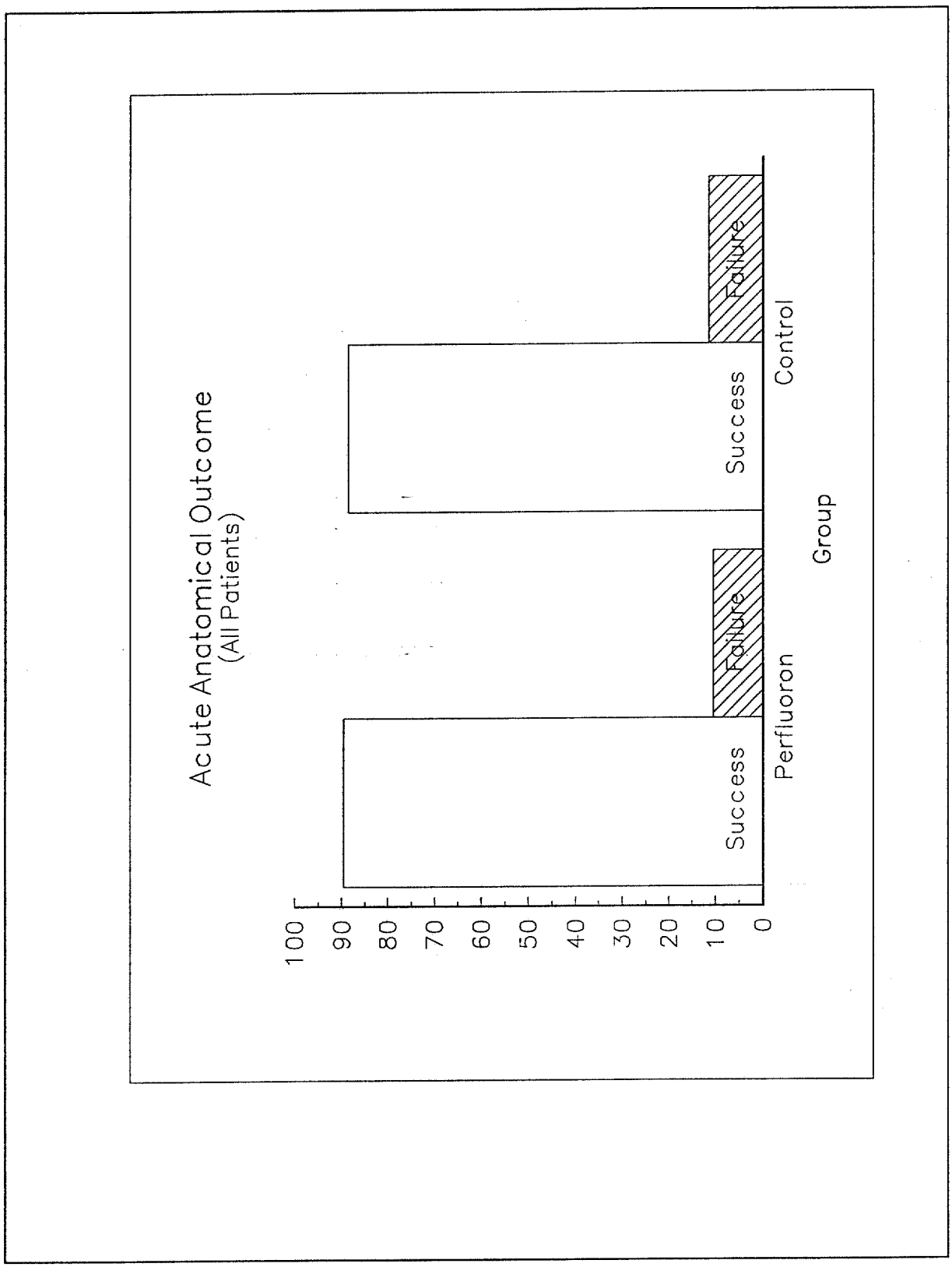
Acute anatomical success was operationally defined as a totally flat retina. Partial attachments and total detachments were classified as acute anatomical failures. Calculations of acute anatomical success were based on all available patients, i.e., "Core" and "Supplemental" patients combined. Overall acute anatomical success was 89.6% (354/395) for PERFLUORON-assisted procedures versus 88.6% (109/123) among the controls.

Acute anatomical success rates were comparable in the PERFLUORON "Core" group (204/226=90.3%) and the PERFLUORON "Supplemental" group (150/169=88.8%). There were no statistically significant differences in acute anatomical success between PERFLUORON-assisted and control procedures when stratified by clinical presentation.

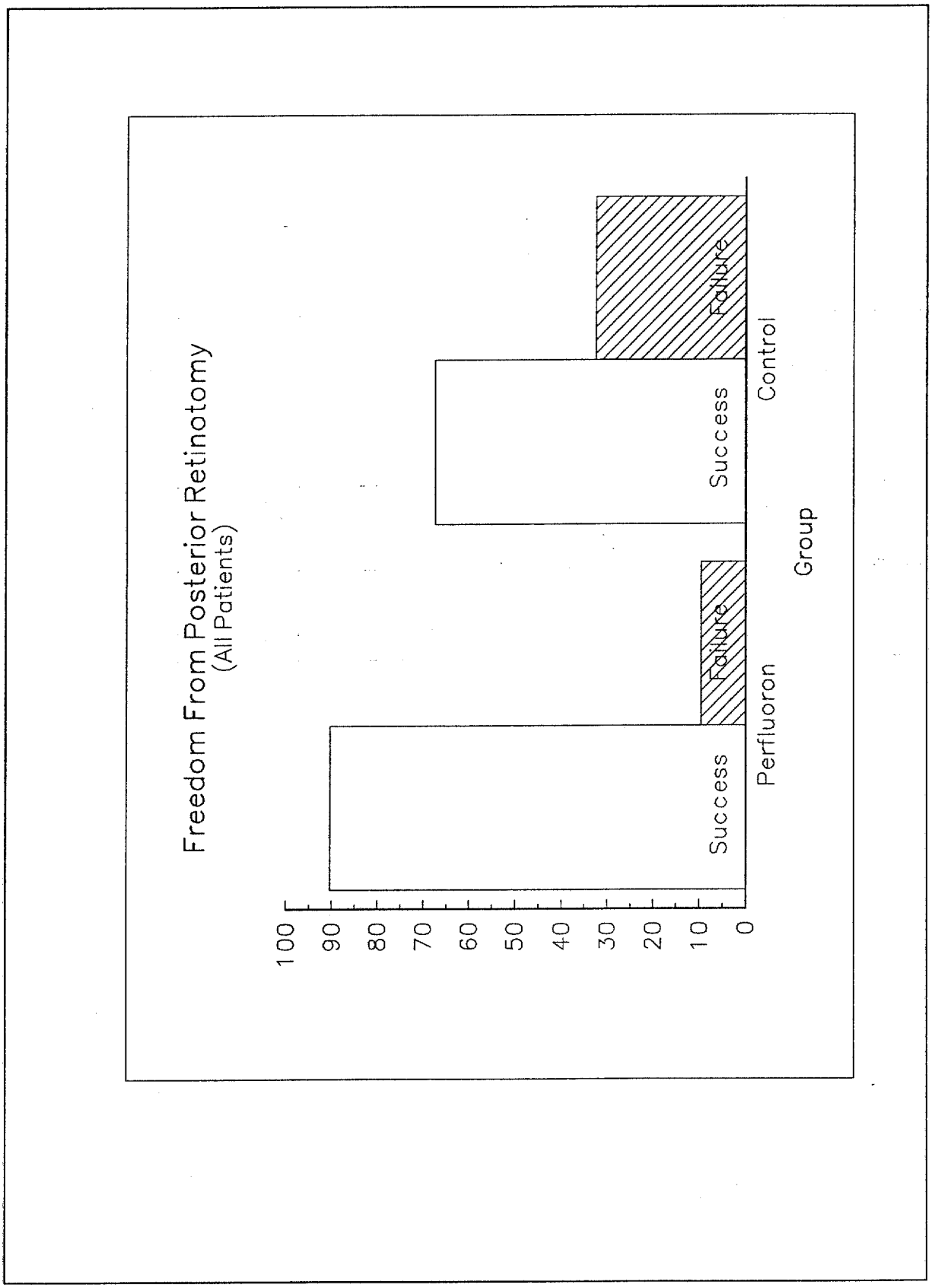
Acute Anatomical Success		
Presentation	PERFLUORON Group	Control Group
TOTAL	89.6% (354/395)	88.6% (109/123)
PVR	91.1% (194/213)	85.9% (55/64)
GRT	92.0% (80/87)	93.3% (14/15)
TRAUMA	83.7% (72/86)	90.9% (40/44)
OTHER	88.9% (8/9)	-

b. Posterior Retinotomy

Calculations regarding posterior retinotomy were based on all available patients. Less than ten percent (38/395=9.6%) of PERFLUORON-assisted procedures required the use of posterior retinotomies compared to 32.5% (40/123) of control procedures. This difference was statistically significant ($p<0.05$). A difference between PERFLUORON and controls was also seen in PVR-related and traumatic detachments ($p<0.05$). The difference for GRT's favored PERFLUORON; however, it was not statistically significant.


Acute Anatomical Outcome
(All Patients)
100
90
80
70
60
50
40
30
20
10
0
Success
Failure
Perfluoron
Success
Failure
Control
Group

Prevalence of Posterior Retinotomy		
Presentation	PERFLUORON Group	Control Group
TOTAL	9.6% (38/395)	32.5% (40/123)
PVR	10.8% (23/213)	34.4% (22/64)
GRT	8.1% (7/87)	13.3% (2/15)
TRAUMA	9.3% (8/86)	36.4% (16/44)
OTHER	0.0% (0/9)	-


Freedom From Posterior Retinotomy
(All Patients)
100
90
80
70
60
50
40
30
20
10
0
Success
Failure
Perfluoron
Success
Failure
Control
Group

6. Postprocedural (Follow-up Data)

a. Duration of Follow-up

Acutely successful "Core" group patients were followed for up to six months whether or not a clinical endpoint was reached. "Clinical endpoints" included: redetachment of the subject retina, enucleation of the perfluoro-n-octane-treated eye, or patient death. One or more follow up evaluations were available for (199/204) of the "Core" group acute successes.

Average Months of Follow up ± Std Dev(#'s)*		
Presentation	PERFLUORON Group	Control Group
Total	6.2 (199/204)	5.9 (109/109)
PVR	6.0±3.4 (119/199)	5.7±2.6 (55/109)
GRT	5.6±2.0 (40/199)	5.4±2.3 (14/109)
TRAUMA	6.4±3.1 (34/199)	6.3±2.3(40/109)

* no follow up for 2 PVR cases (1 dead, 1 pending) and 3 TRAUMA cases (1 enucleated, 1 refused, 1 lost-to-follow) in the PERFLUORON "Core" Group.

b. Freedom From Retinal Redetachment

Calculations regarding redetachment (partial or total) were based on 199 acutely successful "Core" patients. A total of 141 retinal redetachments were reported (PERFLUORON: 78/199 = 39.26%, CTRL: 63/109 = 57.8%) among "core" group acute successes.

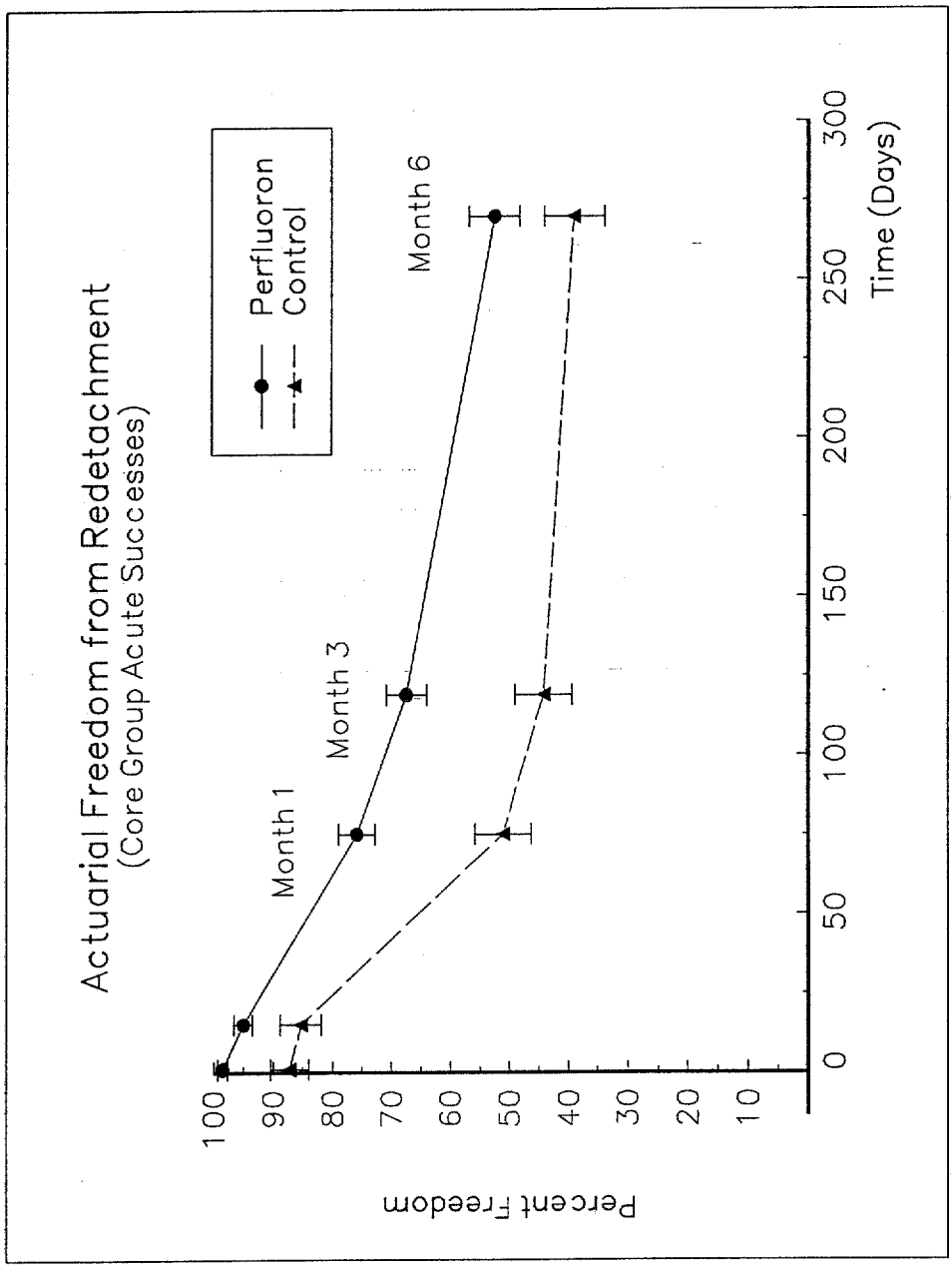
The overall actuarial "6-month" redetachment rate of 47.4% for PERFLUORON - assisted acute successes was lower than the 60.9% rate for controls ($p<0.05$). When stratified by clinical presentation, the difference persisted for PVR and GRT cases, but not for traumatic detachments.

Prevalence of Retinal Redetachment*†		
Presentation	PERFLUORON "Core" Group Acute Successes	Control Group Acute Successes
TOTAL	39.3% (78/199)	57.8% (63/109)
PVR	40.3% (48/119)	54.6% (30/55)
GRT	25.0% (10/40)	57.1% (8/14)
TRAUMA	50.0% (17/34)	62.5% (25/40)
OTHER	50.0% (3/6)	-

* no follow up for 2 PVR cases (1 dead, 1 pending) and 3 TRAUMA cases (1 enucleated, 1 refused, 1 lost-to-follow) in the PERFLUORON Group.
† Cases reported do not include "Others" because no controls exist to which to compare them.

"6-month" Actuarial Incidence of Retinal Redetachment*		
Presentation	PERFLUORON "Core" Group Acute Successes	Control Group Acute Successes
TOTAL	47.4%	60.9%
PVR	49.8%	58.8%
GRT	26.7%	64.2%
TRAUMA	56.6%	62.7%

* no follow up for 2 PVR cases (1 dead, 1 pending) and 3 TRAUMA cases (1 enucleated, 1 refused, 1 lost-to-follow) in the PERFLUORON Group.

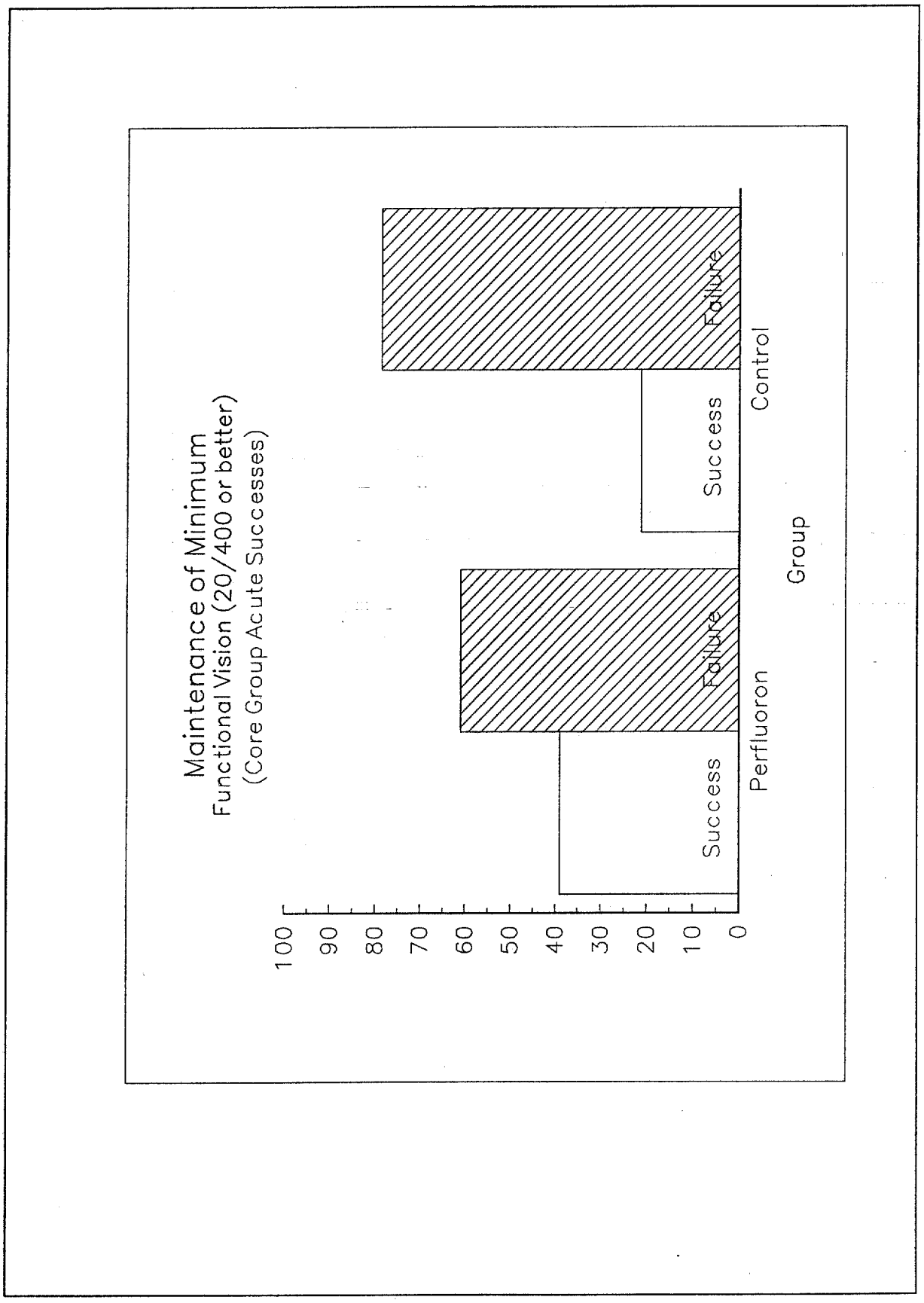

Actuarial Freedom from Redetachment
(Core Group Acute Successes)
Perfluoron
Control
Month 1
Month 3
Month 6
Percent Freedom
Time (Days)
100
90
80
70
60
50
40
30
20
10
0
50
100
150
200
250
300

c. Maintenance of Minimum Functional Vision

Minimum functional vision was operationally defined as visual acuity (VA) equal to 20/400 or better. Calculations were based on the last reported VA for all "Core" group acute successes. Redetachments were classified as having failed to maintain minimum functional vision regardless of the last reported VA. Among PERFLUORON assisted acute successes, 39.0% maintained at least minimum functional vision (74/190) compared with 21.3% in the control group (23/108). This difference was statistically significant ($p<0.05$). The difference persisted for PVR ($P<0.05$), was borderline for GRT ($p<0.08$) and was not significant for traumatic detachments ($p=0.90$).

Maintenance of Minimum Functional Vision*†		
Presentation	PERFLUORON "Core" Group Acute Successes	Control Group Acute Successes
TOTAL	38.9% (74/190)	21.3% (23/108)
PVR	35.4% (40/113)	16.4% (9/55)
GRT	62.2% (23/37)	30.8% (4/13)
TRAUMA	22.9% (8/35)	25.0% (10/40)
OTHER	60.0% (3/5)	-

* no follow up VA for 14 eyes in the PERFLUORON Group and 1 eye in the Control group.
† Cases reported do not include "Others" because no controls exist to which to compare them.


Maintenance of Minimum
Functional Vision (20/400 or better)
(Core Group Acute Successes)
100
90
80
70
60
50
40
30
20
10
0
Success
Failure
Success
Failure
Perfluoron
Control
Group

7. Adverse Reactions and Complications

Two known risks are associated with the use of PERFLUORON. Intraoperatively, PERFLUORON may pass into the subretinal space through a posterior retinal break. The second known risk involves the retention of small amounts of the material anywhere in the eye. Based on animal studies and early clinical experience, perfluoro-n-octane appears to be well tolerated by the eye.

a. Intraoperative Subretinal PERFLUORON Migration

Subretinal PERFLUORON migration was observed in 32 of 395 PERFLUORON-assisted procedures (8.1%). There was no apparent difference in the prevalence of subretinal migration among "pure" PVR's versus GRT's or traumatic detachments. Posterior retinotomies were performed in 28% (9/32) of cases with subretinal migration compared to 8% (29/363) of cases with no migration ($p<0.05$). There was no evidence of postoperative residual PERFLUORON in 27 of 32 (84.4%) procedures with subretinal PERFLUORON migration. Acute anatomical success was achieved in 78% (25/32) of cases with subretinal migration compared to 91% (329/363) of cases with no migration ($p<0.05$).

b. Postoperative Residual PERFLUORON

Postoperative residual PERFLUORON was observed in 25 of 395 PERFLUORON-assisted procedures (6.3%). Residual PERFLUORON appeared to be more common in GRT's versus PVR's or traumatic detachments; however, the difference was not statistically significant.

Potential postoperative implications of residual PERFLUORON were investigated with respect to retinal redetachment, elevated IOP, hypotony, newly acquired cataracts, and last reported ocular status in terms of anterior chamber abnormalities and corneal abnormalities. These analyses were based on 204 PERFLUORON-assisted acute anatomical successes in which postoperative residual PERFLUORON was observed in 14 cases (6.9%) and no residual PERFLUORON was observed in 190 cases.

There were no significant differences between PERFLUORON-assisted cases with residual PERFLUORON versus those with no residual PERFLUORON with respect to retinal redetachment, elevated IOP, hypotony, newly acquired cataracts, or last reported ocular status in terms of anterior chamber abnormalities or corneal abnormalities.

c. Technical/procedural Problems

Intraoperative Retinal Slippage

Intraoperative retinal slippage was observed in 33 of 395 (8.4%) PERFLUORON-assisted cases. Retinal slippage was reported in 18% of GRT cases (16/87), 12% of trauma cases (10/86) and 3% of PVR cases (7/213). These prevalences were statistically significantly different ($p<0.05$).

There were no significant differences between PERFLUORON-assisted cases with retinal slippage versus those with no slippage with respect to retinal redetachment, elevated IOP, hypotony, newly acquired cataracts, or last reported ocular status in terms of anterior chamber abnormalities or corneal abnormalities. These analyses were based on 204 PERFLUORON-assisted acute anatomical successes in which retinal slippage was observed in 11 cases (5.4%) and no slippage was observed in 193 cases.

d. General Vitrectomy Surgical Complications

Postoperative vitrectomy complications include: corneal abnormalities such as epithelial defects and decompensation, increased intraocular pressure, inflammation, endophthalmitis, hemorrhage, cataract formation, recurrent proliferative vitreoretinopathy, retinal redetachment, sympathetic ophthalmia, phthisis bulbi, cystoid macular edema, rubeosis iritis and neovascular glaucoma.

e. General Vitreoretinal Surgical Complications

Corneal abnormalities, the most common being epithelial edema secondary to the intraocular pressure elevation often necessary to control bleeding during dissection of fibrovascular tissue, are a relatively common postoperative finding, but they frequently result from intraoperative mechanical or toxic insults.

Direct damage to the crystalline lens (cataract) during vitreous surgery can occur but it is relatively uncommon.

Iatrogenic retinal breaks are a frequent complication of vitreous surgery, occurring in up to 69% of eyes with complicated retinal detachments from proliferative diabetic retinopathy.

The incidence of retinal incarceration as a complication of vitreoretinal surgery is uncommon and is usually encountered as a result of penetrating trauma rather than the surgery itself.

The reported incidence of significant choroidal hemorrhage varies. One study reported a 1.9% incidence of operative or immediately postoperative choroidal hemorrhage for vitreous surgery. The study identified four risk factors: placement of a scleral buckle, elevated preoperative IOP, increased age, and nonphakic lens status. This figure is higher than the risk reported for intraocular surgery in general (0.7%) or for cataract surgery in particular (0.2%).

Intraoperative bleeding is the only major complication that has become more frequent despite improvements in vitreous surgical instrumentation and technique. This is probably due to the changing indications for surgery, especially in diabetic retinopathy, where eyes with extensive, active neovascularization may require significant epiretinal tissue dissection.

Intraoperative hypotony can lead to significant complications that can hinder the normal

In order to control or prevent significant intraocular hemorrhaging, it is often necessary to elevate infusion pressure to supranormal levels which can occasionally lead to central retinal artery occlusion.

f. General Postoperative Complications

Postoperative nonhealing or slowly healing epithelial defects are most common in diabetic eyes, with estimates of 3% to 9% for this problem in patients undergoing vitrectomy for complications of diabetic retinopathy. Risk is further increased by pars plana lensectomy or a history of previous vitreous surgery.

The development or progression of cataract is the most common long-term complication following vitrectomy for phakic eyes. This condition is found in up to 75% of eyes followed for 10 or more years.

The incidence of postvitrectomy fibrin formation ranges from 5% to 22%; it is more commonly seen after surgery in diabetic eyes.

Ocular inflammatory response is a necessary and unavoidable part of the healing process.

The reported incidence of postoperative retinal detachment varies between 14% and 36%. In complicated cases, inflammation with fibrin membrane deposition and recurrent PVR leading to traction retinal detachment are the most common mechanisms for anatomical failure.

Significant intraocular pressure elevation has been reported in 9% of eyes receiving C_3F_8 gas versus 13% receiving silicone oil for internal retinal tamponade at the conclusion of surgery for PVR.

The incidence of postoperative vitreous hemorrhage for all cases is about 6%. This figure is higher in eyes that have undergone vitrectomy for complications of proliferative diabetic retinopathy, where reports vary between 11% and 60%.

g. Complications of Surgery for Proliferative Vitreoretinopathy

The most common complications in surgery for PVR are postoperative; their common pathogenic mechanism is fibrin and scar tissue reproliferation. The main cause for anatomic failure after surgery for PVR is new or recurrent anterior PVR leading to retinal redetachment or hypotony. Redetachment rates vary depending on the initial cause for the detachment and the severity of the PVR. In mild to moderately complicated cases (with little or no anterior component), redetachment from recurrent PVR occurs in 30% to 40% of eyes, but the figure may be as high as 60% after surgery for severe PVR with pronounced anterior proliferation. The material selected for postoperative retinal tamponade may affect the likelihood of retinal redetachment, as demonstrated in the reports of the Silicone Oil Study Group[5].

h. Complications of Surgery for Traumatic Retinal Detachments

Vitreoretinal surgery for ocular trauma is a complex topic because of the wide variability of causative factors and their resulting injuries. Penetrating injuries with or without intraocular foreign bodies ("IOFB's") are one of the more common types of trauma encountered by the vitreoretinal surgeon. Surgical complications related to removal of posterior segment IOFB's are related to technique and location of the foreign body. They include: retinal or lens damage secondary to movement of the foreign body, retinal detachment due to removal of an IOFB that has penetrated the retina but not the posterior sclera, and intraocular hemorrhage on disturbing recently traumatized tissues.

i. Complications of Surgery for Giant Retinal Tears (GRT)

The complications most often encountered during or vitreoretinal surgery for GRT's include:

1. Cataract formation or progression (6%-9%)
2. Macular pucker (up to 34%)
3. Recurrent redetachment (9%-22%)
4. PVR (10%-25%)
5. Subretinal migration of air or other materials used to reattach the retina.

j. Statistical Analyses of Other Ocular Complications

Statistical analyses of other ocular complications were based on 313 acute successes in the "Core" group (204 PERFLUORON-assisted, 109 unassisted controls).

(1) "No light perception" (NLP) Eyes

A total of 31 eyes were observed to have had visual acuity reduced to NLP at one or more postoperative evaluations (23 "Core", 8 "Supplemental"). There was no significant difference in the incidence of NLP visual acuity among PERFLUORON-assisted procedures (9/204 = 4.4%) versus controls (7/109 = 6.4%).

(2) Anterior Chamber Abnormalities

Based on acutely successful core group patients, anterior chamber abnormalities were observed in 34% (70/204) of PERFLUORON-assisted procedures versus 32% (35/109) of controls. This difference was not statistically significant.

(3) Post-procedure Cataract Formation

Based on acutely successful core group patients, post-procedure cataracts were observed in 6% (12/204) of PERFLUORON-assisted procedures versus 4% (4/109) of controls. This difference was not statistically significant.

(4) Elevated IOP

Based on acutely successful core group patients, elevated IOP was observed in 18% (37/204) of PERFLUORON-assisted procedures versus 17% (18/109) of controls. This difference was not statistically significant.

(5) Hypotony

Based on acutely successful core group patients, hypotony was observed in 15% (31/204) of PERFLUORON-assisted procedures versus 16% (17/109) of controls. This difference was not statistically significant.

(6) Corneal Abnormalities

Based on acutely successful core group patients, corneal abnormalities were observed in 46% (93/204) of PERFLUORON-assisted procedures versus 39% (42/109) of controls. This difference was not statistically significant.

(7) Iris Abnormalities

Based on acutely successful core group patients, iris abnormalities were observed in 15% (31/204) of PERFLUORON-assisted procedures versus 18% (20/109) of controls. This difference was not statistically significant.

8. Age and Gender Bias

Age and Gender distributions were comparable (no significant difference) for the PERFLUORON-assisted group versus the control group. There was no apparent relationship between age, gender, or age/gender and acute anatomical success, posterior retinotomy rates, redetachment rates, or maintenance of minimum functional vision.

9. Type of Postoperative Tamponade

The proportion of subjects receiving gas or silicone oil as the tamponade agent was comparable for the PERFLUORON-assisted group (51% gas, 42% oil) versus the control group (56% gas, 43% oil). Among those subjects in whom gas was used, the majority of the cases were managed with C_3F_8 for both the PERFLUORON-assisted group (88%) and the control group (84%).

In light of the similarity of the PERFLUORON-assisted group and the control group with respect to postoperative tamponade, it is unlikely that differences between these groups can be attributed to this factor.

10. Outcome of Retinal Detachment Surgeries Between Centers

There was no statistically significant difference with respect to acute success, posterior retinotomy, redetachment, or maintenance of minimum functional vision in

PERFLUORON-assisted surgeries from investigational sites which contributed control data versus the other sites.

11. Patient Discontinuation and Explanation

22 "core" group patients who did not experience a clinical endpoint were discontinued from the investigations prior to their "6 month" follow-up visit.

12. Patient Complaints

No patient complaints were reported.

13. Device Failures and Replacements

No device failures or replacements were reported.

14. Statistical Analyses of the Clinical Investigations

For certain statistical analyses, PERFLUORON-assisted procedures ("PERFLUORON group") were stratified into two groups based on initial procedure date. The "PERFLUORON core group" ("CORE") included all patients initially treated on or before 4/13/94 (n=226) and the "PERFLUORON supplemental group" ("SUPP") included all subsequent cases through 10/24/94 (n=169). Analyses of acute outcomes were based on the "Core" group and "Supplemental" group combined, i.e. all PERFLUORON-assisted procedures. Analyses of chronic outcomes and events were based on the "Core" group.

Results of statistical analyses are summarized below:

- There was no statistically significant difference in overall acute anatomical success for PERFLUORON-assisted procedures (89.6%, 354/395) versus control procedures (88.6%, 109/123).

- There were statistically significantly fewer posterior retinotomies associated with PERFLUORON-assisted procedures (9.6%, 38/395) versus control procedures (32.5%, 40/123).

- The overall rate of retinal redetachment was statistically significantly lower among PERFLUORON-assisted acutely successful procedures (39.3%, 78/199) versus control procedures (57.8%, 63/109).

- The proportion of procedures in which minimum functional vision was maintained was higher among PERFLUORON-assisted acutely successful procedures (39%, 74/190) versus control procedures (21.3%, 23/108).

- Subretinal PERFLUORON migration was observed in 32 of 395 PERFLUORON-assisted procedures (8.1%). There was no apparent difference in the prevalence of subretinal migration among "pure" PVR's versus GRT's or traumatic detachments.

Posterior retinotomies were performed in 28% (9/32) of cases with subretinal migration compared to 8% (29/363) of cases with no migration ($p<0.05$). There was no evidence of postoperative residual PERFLUORON in 27 of 32 (84.4%) procedures with subretinal PERFLUORON migration. Acute anatomical success was achieved in 78% (25/32) of cases with subretinal migration compared to 91% (329/363) of cases with no migration ($p<0.05$).

- Postoperative residual PERFLUORON was observed in 25 of 395 PERFLUORON-assisted procedures (6.3%). Residual PERFLUORON appeared to be more common in GRT's versus PVR's or traumatic detachments; however, the difference was not statistically significant. There were no significant differences between PERFLUORON-assisted cases with residual PERFLUORON versus those with no residual PERFLUORON with respect to retinal redetachment, elevated IOP, hypotony, newly acquired cataracts, or last reported ocular status in terms of anterior chamber abnormalities or corneal abnormalities.

- Intraoperative retinal slippage was observed in 33 of 395 (8.4%) PERFLUORON-assisted cases. Retinal slippage was reported in 18% of GRT cases (16/87), 12% of trauma cases (10/86) and 3% of PVR cases (7/213). These prevalences were statistically significantly different ($p<0.05$). There were no significant differences between PERFLUORON-assisted cases with retinal slippage versus those with no slippage with respect to retinal redetachment, elevated IOP, hypotony, newly acquired cataracts, or last reported ocular status in terms of anterior chamber abnormalities or corneal abnormalities.

- Based on acutely successful "core" group patients, there was no significant difference between PERFLUORON-assisted cases and controls with respect to other postoperative complications such as: NLP eyes, anterior chamber abnormalities, cataract formation, elevated IOP, hypotony, corneal abnormalities or iris abnormalities.

IX. CONCLUSIONS DRAWN FROM THE CLINICAL STUDIES

A. Discussion of Valid Scientific Evidence

In accordance with 21 C.F.R. §860.7 the validity of the evidence presented in the Premarket Approval (PMA) was based upon an objective trial with a matched control. The study comprised a prospective, multi-center, non-randomized, open label clinical trial. Clinical results were compared to an historical control group derived from patient charts at four of the participating centers.

The evidence supporting the reasonable assurance of safety and effectiveness from the clinical study conducted with PERFLUORON was:

	PERFLUORON	Control Group
Total Number of Eyes Treated "Core" eyes treated 4/20/92 thru 4/13/94	All Eyes - 395 "Core" - 226	123
Acute Retinal Attachment Rate (All Eyes)	89.6% (354/395)	88.6% (109/123)
Posterior Retinotomy Required (All Eyes)	9.6% (38/395)	32.5% (40/123)
Acute Retinal Attachment Rate (Core)	90.3% (204/226)	88.6% (109/123)
Average Follow-up of Acute Successes (months) (Core)	6.2 (199/204)	5.9 (109/109)
Retinal Redetachment Rate (Core)	39.3% (78/199)	57.8% (63/109)
Maintenance of Minimum Functional Vision (Core)	38.9% (74/190)	21.3% (23/108)

B. Benefits of PERFLUORON

1. **Mechanical tool during vitreoretinal surgery.** PERFLUORON acts as a mechanical tool, providing hydrokinetic manipulation, flattening, smoothing, and/or unrolling of the detached retinal membrane starting from the posterior aspect, and/or creating gentle traction on epiretinal membranes, thus facilitating their visualization.

2. **Anterior displacement of subretinal fluids.** PERFLUORON facilitates the anterior displacement of subretinal fluids and reduces the incidence of posterior drainage retinotomies during the repair of rhegmatogenous retinal detachments.

3. **Intraoperative tamponade.** PERFLUORON provides temporary mechanical fixation of the retina against the choroid to allow application of thermal adhesive modalities.

C. Risks of PERFLUORON

1. **General Health.** There have been no reports of intraocular PERFLUORON causing any adverse event as related to the general health of the patient.

2. **Ocular complications.** The clinical studies with PERFLUORON established that additional risks added to the surgical procedure were minor. The two PERFLUORON-associated risks, intraoperative subretinal PERFLUORON Migration (8.1%) and postoperative Residual PERFLUORON (6.3%) do not add major risks to the surgery. Removal of the subretinal PERFLUORON can be achieved by aspiration through an existing retinal break or by creation of a posterior retinotomy. Comparing cases of residual PERFLUORON with no residual, there were no significant differences with respect to retinal redetachment, elevated IOP, hypotony, newly acquired cataracts, or last reported ocular status in terms of anterior chamber abnormalities or corneal abnormalities.

There was no evidence from the clinical trial that known postoperative complications of complicated retinal detachment surgery were higher when PERFLUORON was used. Based on acutely successful "core" group patients, there was no significant difference between PERFLUORON-assisted cases and controls with respect to: NLP eyes, anterior chamber abnormalities, cataract formation, elevated IOP, hypotony, corneal abnormalities or iris abnormalities.

D. Conclusion

In conclusion, the relative benefit/risk ratio for PERFLUORON was weighed based on the following:

1. an acceptable chance for restoration or maintenance of ambulatory vision;

2. statistically significantly fewer posterior retinotomies and statistically significantly lower rates of retinal redetachment associated with PERFLUORON-assisted procedures versus control procedures; and,

3. a higher proportion of procedures in which minimum functional vision was maintained among PERFLUORON-assisted acutely successful procedures versus control procedures.

Therefore, it is reasonable to conclude that the benefits of use of the device for the target population outweigh the risk of illness or injury when used as indicated in accordance with the directions for use.

X. PANEL RECOMMENDATION

At an advisory meeting on October 19, 1995, the Ophthalmic Devices Panel recommended that Infinitech's PMA for PERFLUORON be approved without conditions.

XI. CDRH DECISION

PERFLUORON was granted EXPEDITED REVIEW status on June 14, 1995. Expedited review status was granted for the following reasons: (a) this device, a perfluorocarbon liquid, is indicated for use as an intraoperative retinal tamponade in cases of complex retinal detachment; if left untreated, these types of detachment potentially lead to blindness within six months; (b) properties of perfluorocarbon liquids provide the potential for an improved intraoperative tool to flatten the retina and to manipulate an inverted posterior retinal flap; and, (c) there are currently no perfluorocarbon liquids approved for marketing. CDRH concurred with the Ophthalmic Devices Panel's recommendation of October 19, 1995, and issued a letter to Infinitech, on November 17, 1995, advising that its PMA was approvable subject to Infinitech's submission of additional microbiological information and subject to Infinitech's agreement on final labeling. In an amendment received by FDA on

November 30, 1995, Infinitech submitted the required data. Infinitech's amendment received by FDA on February 16, 1996, provided the final draft labeling for the device. The data and the labeling were acceptable. FDA issued an approval order on FEB 29 1996.

The sponsor's manufacturing facility was inspected on November 8, 1995, and was found to be in compliance with the device Good Manufacturing Practice regulations.

XII. APPROVAL SPECIFICATIONS

Directions for Use - See the labeling (Attachment 1).

Hazards to Health from Use of the Device - See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the labeling (Attachment 1).

Postapproval Requirements and Restrictions: See approval order (Attachment 2).

REFERENCES

1. Chang S, Lincoff H, Zimmerman NJ, and Fuchs W. *Giant Retinal Tears: Surgical Techniques and Results Using Perfluorocarbon Liquids.* Arch. Ophthalmol 107: 761-766 (1989).

2. Chang S. *Giant Retinal Tears: Surgical Management with Perfluorocarbon Liquids.* Medical and Surgical Retina. Lewis and Ryan, editors. Mosby Yearbook, New York (1994).

3. Chang S, Ozmert E, Zimmerman NJ, and Fuchs W. *Intraoperative Perfluorocarbon Liquids in the Management of Proliferative Vitreoretinopathy.* Am. Journal Ophthalmol. 106: 668-674 (1988).

4. Chang S, Reppucci V, Zimmerman NJ, Heinemann MH, Coleman DJ. *Perfluorocarbon Liquids in the Management of Traumatic Retinal Detachments.* Ophthalmology 96:785-792 (1989).

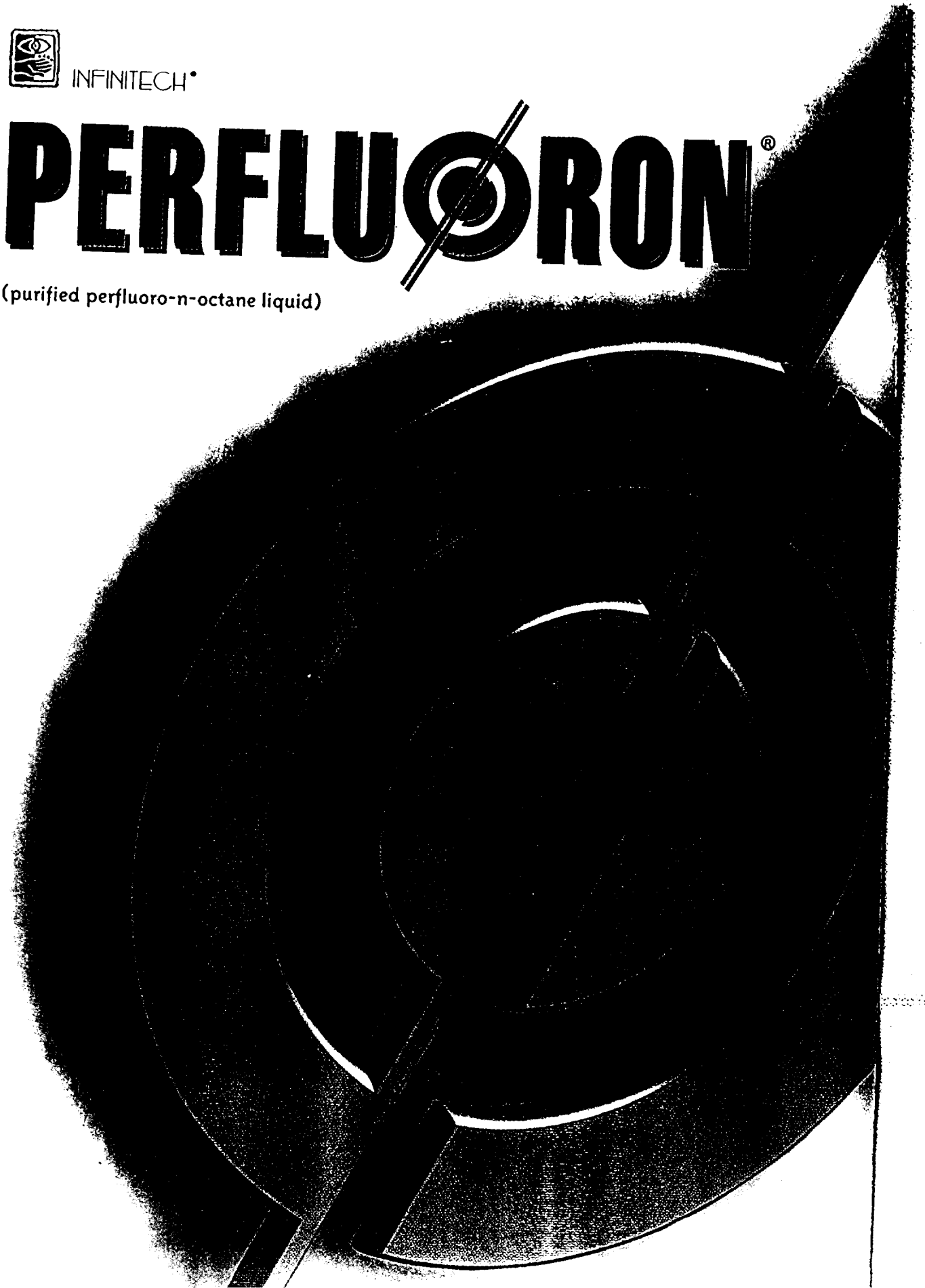
5. The Silicone Oil Study Group. *Vitrectomy with Silicone Oil or Sulfur Hexafluoride Gas in Eyes with Severe Proliferative Vitreoretinopathy: Results of a Randomized Clinical Trial.* Arch. Ophthalmol. 110:770-779 (1992).

ATTACHMENT 1

INFINITECH®

PERFLUORON®

(purified perfluoro-n-octane liquid)

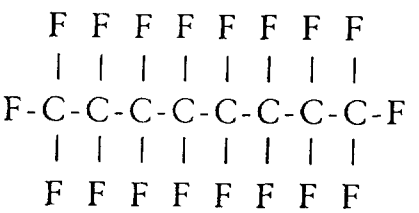


PERFLUORON® R_x
(purified perfluoro-n-octane liquid)

DESCRIPTION

PERFLUORON® (purified perfluoro-n-octane liquid) is sterile, non-pyrogenic, purified perfluoro-n-octane (≥99.9% PFNO) for temporary use as a mechanical tool during vitreoretinal surgery. Perfluoro-n-octane is a member of the perfluorocarbon chemical family, chemicals composed of carbon and fluorine atoms. Perfluorocarbons exhibit high oxygen solubility and are relatively inert substances with little biological toxicity potential.

The structure of the molecule is:



C_8F_{18} or $CF_3(CF_2)_6CF_3$
(CAS No. 307-34-6)

PERFLUORON is optically clear, has a high vapor pressure and low viscosity, and has a lower refractive index and a much higher specific gravity than aqueous. It is inert and immiscible in water, ionic solutions and common organic chemicals.

The chemical and physical properties of PERFLUORON are listed below.

Molecular Weight	438
Specific Gravity	1.754
Surface Tension (dynes/cm, 27.2°C)	16.98
Refractive Index	1.27
Vapor Pressure (mm Hg. @ 37°C)	52
Viscosity (centistoke @ 25°C)	0.69

PERFLUORON contains no preservatives or other ingredients.

PERFLUORON is supplied in a kit containing a 5ml vial of PERFLUORON, together with: a) one Millipore Millex-FG, 0.2 µm microbial filter unit, b) one B-D 10cc syringe, c) one 20 gauge x 1½" beveled needle, and d) one 23 gauge blunt cannula. All components are sterile in individual sterile packages, but the lidded tray is *not sterile.*

INDICATIONS FOR USE

PERFLUORON is an intraoperative tool indicated for use during vitreoretinal surgery in patients with primary or recurrent retinal detachment which is complicated by penetrating ocular trauma, giant retinal tear(s) or proliferative vitreoretinopathy (PVR).

CONTRAINDICATIONS

- PERFLUORON is contraindicated for long-term use in the eye or as a vitreous replacement.

WARNINGS

- PERFLUORON should not be injected directly into the vitreous, or injected simultaneously with aspiration of the vitreous, as severe intraocular damage may occur.
- At the conclusion of the surgical procedure, PERFLUORON must be completely removed from the eye, and replaced with an appropriate vitreous substitute.

PRECAUTIONS

- Directions for Use of PERFLUORON should be followed closely.
- Subretinal migration, or placement, of PERFLUORON may occur during the injection of the device. (See Directions for Use)
- The safety and effectiveness of the use of PERFLUORON in patients under 15 months of age has not been established.
- During the clinical trials, posterior retinal slippage occurred at the anterior edge of the giant retinal tear in 18% of patients with Giant Retinal Tears. (See Directions for Use)
- To avoid inadvertent placement of PERFLUORON behind the retina during injection, the final fill level in the eye should always remain posterior to any large retinal breaks.
- If PERFLUORON is introduced into a large retinal break, it may slip into the subretinal space. Special care should be taken to examine for and remove any subretinal PERFLUORON through an existing posterior tear or through a posterior retinotomy prior to the completion of surgery. (See Directions for Use)
- Do not resterilize PERFLUORON.
- Do not admix PERFLUORON with any other substances prior to use.
- Do not use PERFLUORON after its expiration date.

ADVERSE REACTIONS AND COMPLICATIONS

Adverse Events reported during the clinical trial of PERFLUORON include enucleation (3 eyes, 1 day to 1 month

following surgery), heart attack (1 patient, 8 days following surgery) and death (1 patient, greater than 3 months after surgery). None were considered to be associated with the use of PERFLUORON.

The following adverse reactions related to the use of PERFLUORON were observed during the clinical trials (These rates of complications may be influenced by the duration of follow-up in the clinical trials):

- Intraoperative Subretinal PERFLUORON Migration 8.1%
- Postoperative Residual PERFLUORON 6.3%

Other complications reported by the investigators are general complications of complicated vitreoretinal surgery, and were not associated specifically to the use of PERFLUORON:

- Corneal Abnormalities 46%
- Anterior Chamber Abnormalities 34%
- Elevated IOP 18%
- Hypotony 15%
- Iris Abnormalities 15%
- Cataract Formation in Phakic Eyes 13.8%
- Intraoperative Retinal Slippage 8.4%
- Progression to "No Light Perception" (NLP) 4.4%

DIRECTIONS FOR USE

5ml of PERFLUORON is supplied per vial. That volume is adequate for an average eye, but highly myopic eyes may require a larger volume.

Do Not Resterilize PERFLUORON

Assembly Instructions

Caution: The components in the tray are packaged in sterile barrier unit packaging. The outer surfaces of these packages, including the PERFLUORON vial, are not sterile, and routine sterile transfer techniques should be followed in preparing the device for use.

Sterile Transfer

1. Remove the PERFLUORON vial from the tray and place it in a stable location, outside the sterile field.
2. Open each remaining component and pass it into the sterile field using routine procedure for sterile transfer.

3. Perform assembly of components in the sterile field.

Assembly

1. Connect the 0.2 micron filter unit to the 10cc disposable syringe.

2. Place the 20 gauge beveled needle securely on the end of the filter unit. The syringe is ready to fill with PERFLUORON.

3. **Caution: The outer surface of the PERFLUORON vial is not sterile and the vial should not be introduced into the sterile field.**

4. Hold the PERFLUORON vial firmly, within reach of the sterile field, and introduce the 20 gauge beveled needle into the vial to withdraw the PERFLUORON.

5. After the PERFLUORON has been completely transferred to the syringe, withdraw the needle from the vial.

6. Remove the 20 gauge needle and filter unit from the syringe and dispose of properly.

7. Securely place the 23 gauge blunt cannula on the syringe. The PERFLUORON is now ready to be used. The syringe may be stored temporarily with the cannula pointed upward to avoid loss of material.

8. Discard the syringe and any unused PERFLUORON remaining in it at the conclusion of the procedure.

All Components for Single Use Only
Do Not Resterilize

The Use of PERFLUORON

Properties

PERFLUORON, by virtue of its high specific gravity, functions as a mechanical tool during vitreoretinal surgery, providing hydrokinetic manipulation of the detached retina. This high specific gravity allows PERFLUORON to be infused over the posterior portion of the retina and facilitates retinal flattening and anterior displacement of subretinal fluid.

PERFLUORON has a significantly different refractive index than Aqueous (1.27 vs 1.33) which assists intraocular visualization and control of the device. It is optically clear, and does not interfere with visualization of the retina.

PERFLUORON is immiscible with water, ionic solutions, and common organic chemicals. It tends to form into droplets, rather than dispersing. These physical properties make it easy to observe during surgery, and to remove by aspiration at the conclusion of the intraoperative procedure.

PERFLUORON has a high vapor pressure which facilitates removal of residual material remaining after aspiration. At room temperature, during the fluid-gas exchange procedure at the conclusion of surgery, any remaining portion of the device will usually evaporate and exit through the sclerotomy sites.

Toxicity and Metabolism

PERFLUORON is a biologically inert substance. There are no known biological enzymes which metabolize the carbon-fluoride bonds in perfluorocarbons.

In a series of *in vitro* and *in vivo* tests, PERFLUORON has been shown to be non-toxic, non-hemolytic, non-pyrogenic, non-mutagenic, and non-irritating. In a retinal and intraocular tolerance study, it was shown to be well-tolerated following short term exposure, but poorly-tolerated following extended term exposures.

General Use

PERFLUORON should be slowly injected over the optic disc to flatten the retina posteriorly. As the retina is flattened, examine it for areas of residual membranes, for traction remaining on the retina and for the presence of previously undetected posterior breaks. Such membranes should be removed or peeled to the extent possible. If large posterior breaks are detected, additional application of PERFLUORON should be discontinued. If no large posterior breaks are present, PERFLUORON should be infused up to the level of the most posterior retinal break, forming a "bubble" in the posterior portion of the retina.

The weight of PERFLUORON on the posterior retina displaces subretinal fluids anteriorly, resulting in a flattened retina up to the edge of the most posterior break. Membrane removal, if necessary, is performed in the aqueous phase with PERFLUORON providing mechanical stabilization of the posterior retina. Areas of residual traction which cannot be freed by dissection may be subject to retinotomy anterior to the bubble. Thermal adhesive treatment can be applied to the edges of the flattened retina through the bubble. If the edge of the tear is too peripheral for endophotocoagulation, transcleral cryotherapy can be applied.

Air-fluid exchange is then performed. With the use of a flute needle, infusion fluid above the bubble should be removed as completely as possible by using air to flatten the anterior retina and displace all anterior subretinal fluid before removal of the PERFLUORON. Endophotocoagulation to the anterior retina should be applied, as indicated.

If PERFLUORON is introduced into a large retinal break, it may slip behind the retinal detachment. This event can be handled by the complete aspiration of the device with either a 20 or 23 gauge cannula, utilizing the break through which it originally migrated. If aspiration at the primary break site does not provide complete removal, a retinotomy should be performed to remove all PERFLUORON.

Occasionally, PERFLUORON may be inadvertently dispersed during injection, resulting in small bubbles (droplets) that are not identified and completely aspirated at the conclusion of surgery. Dispersion of the PERFLUORON can be best controlled by keeping the 23 gauge blunt cannula recommended for injection in the middle of the PERFLUORON bubble as more of the device is injected, and away from the tip of any active infusion cannula.

During the clinical trials, residual droplets of PERFLUORON were occasionally observed in either the anterior or posterior chamber postoperatively. These droplets were not associated with any adverse reactions or complications, but if the situation does arise, it may be necessary to remove the residual PERFLUORON by surgery.

In GIANT RETINAL TEARS:

PERFLUORON should be injected with the patient in the supine position to gently unfold the flap of the tear, and to flatten the retina against the choroidal surface.

If epiretinal membranes are present, they should be removed from both surfaces of the retina, as completely as possible, by conventional means. A small amount of PERFLUORON (0.8 to 1.0ml) should then be injected over the optic disc. As any additional epiretinal membranes are exposed and removed, more PERFLUORON can be slowly injected up to the edge of the tear.

Once the retina is unfolded and the tear is positioned, an appropriate thermal adhesive modality should be applied, through the PERFLUORON, along the edge of the tear. A scleral buckle may be placed before the PERFLUORON is removed.

Remove the PERFLUORON at the conclusion of the procedure by aspiration through either a 23 gauge or flute needle during the air/fluid exchange.

During the clinical trials, posterior retinal slippage occurred at the equator of the giant retinal tear in 18% of patients with

Giant Retinal Tears. To reduce the potential for the edge of the flap to move posteriorly, carefully remove all saline at the edge of the break before proceeding with the aspiration of PERFLUORON posteriorly. This maneuver reduces the chance of slippage by removing subretinal fluids that might otherwise tend to flow posteriorly. Retinal slippage, if it occurs during the fluid-air exchange, can be corrected by replacing some of the air with saline solution and by using an expanding gas concentration after turning the patient into the appropriate position postoperatively.

When gas tamponade is chosen, an automated air infusion system should be used during fluid-air exchange. A flute or extrusion needle with a soft silicone tip may be used, being placed first near the margin of the tear. As the air bubble descends, it flattens the anterior retina, expressing the subretinal fluid through the break. All saline at the edge of the break should be carefully removed before proceeding to aspirate the PERFLUORON posteriorly. This maneuver reduces the chance of slippage of the posterior flap.

The intrinsic elasticity of the detached retina may result in extensive slipping and retinal folding under air. When this occurs, the air should be replaced by balanced saline, and the PERFLUORON re-injected to reposition the retinal detachment. When the tear is repositioned, direct exchange of PERFLUORON for silicone oil, which engages the edge of the tear as it descends, will prevent slippage and folding of the retina.

When silicone oil is selected for extended tamponade, the PERFLUORON may be directly aspirated as the silicone oil is injected with an automated infusion pump. When the silicone oil is first injected, a soft-tipped flute or extrusion needle is placed anteriorly near the edge of the tear to aspirate all saline anterior to the PERFLUORON. When the silicone bubble contacts the PERFLUORON, the interface is visible and the PERFLUORON is aspirated in an anterior-to-posterior direction.[2]

When silicone oil is selected for extended retinal tamponade, small droplets of PERFLUORON may be difficult to distinguish from air bubbles that have become mixed with the silicone oil during its infusion. However, within seconds, air bubbles will float anteriorly in the silicone oil, while the small PERFLUORON droplets will descend onto the surface of the retina, making them easier to identify and aspirate.[2]

In PROLIFERATIVE VITREORETINOPATHY (PVR)[3]

PERFLUORON is a useful intraoperative instrument for the hydrokinetic manipulation of the retina during vitrectomy surgery for proliferative vitreoretinopathy. PERFLUORON permits manipulation of the retina with the patient in the supine position.

After epiretinal membrane dissection and removal of all visible posterior preretinal membranes, inject the PERFLUORON into the funnel of the retinal detachment, positioned directly above the optic disc. Areas of residual traction and membranes may be exposed as the PERFLUORON fills the posterior chamber. The PERFLUORON interface should be kept posterior to these areas, and epiretinal membranes removed in a posterior to anterior direction. More PERFLUORON may be injected as needed, up to the level of the most posterior retinal break.

In OCULAR TRAUMA[4]

Penetrating ocular trauma elicits a broad range of ocular responses, including intraocular bleeding, severe inflammation, fibrous proliferation, scarring, and cyclitic membrane formation. Retinal detachment may result from these processes or from the injury itself.

PERFLUORON is a useful intraoperative tool during vitreoretinal surgery in the repair of severe ocular trauma, using the techniques described previously for hydrokinetic manipulation of the retina.

Post-Procedure

PERFLUORON **must be removed** at the conclusion of the procedure by aspiration through either a 23 gauge or flute needle during the air/fluid exchange (see WARNINGS).

HOW SUPPLIED

PERFLUORON is sterile, single-use, non-pyrogenic, purified perfluoro-n-octane liquid, packaged in a 5ml unit dose container.

Each packaged tray unit also contains the following:

- A sterile single-use 23 gauge blunt cannula.
- A sterile single-use 0.2 micron filter unit.
- A sterile single-use 10cc luer-lock syringe.
- A sterile single-use 20 gauge beveled needle.
- A Package Insert.

For intraocular use only.

REFERENCES

1. Chang S, Lincoff H, Zimmerman NJ, and Fuchs W. *Giant Retinal Tears: Surgical Techniques and Results Using Perfluorocarbon Liquids.* Arch. Ophthalmol 107: 761-766 (1989).

2. Chang S. *Giant Retinal Tears: Surgical Management with Perfluorocarbon Liquids.* Medical and Surgical Retina. Lewis and Ryan, editors. Mosby Yearbook, New York (1994).

3. Chang S, Ozmert E, Zimmerman NJ, and Fuchs W. *Intraoperative Perfluorocarbon Liquids in the Management of Proliferative Vitreoretinopathy* Am. Journal Ophthalmol. 106: 668-674 (1988).

4. Chang S, Reppucci V, Zimmerman NJ, Heinemann MH, Coleman DJ. *Perfluorocarbon Liquids in the Management of Traumatic Retinal Detachments.* Ophthalmology 96:785-792 (1989).

Manufactured in the U.S.A. by Infinitech, Inc.
Chesterfield, MO 63005

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

Mr. L.E. Mosher
Vice.President
Infinitech Inc.
750 Goddard Avenue
Chesterfield, MO 63005

FEB 29 1996

RE: P950018
Perfluoron® (purified perfluoro-n-octane liquid)
Filed: April 28, 1995
Amended: September 5 and November 30, 1995 and February 16, 1996

Dear Mr. Mosher:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your premarket approval application (PMA) for Perfluoron® (purified perfluoro-n-octane liquid). This device, a perfluorocarbon liquid, is an intraoperative tool indicated for use during vitreoretinal surgery in patients with primary or recurrent retinal detachment which is complicated by penetrating ocular trauma, giant retinal tear(s) or proliferative vitreoretinopathy (PVR). We are pleased to inform you that the PMA is approved subject to the conditions described below and in the "Conditions of Approval" (enclosed). You may begin commercial distribution of the device upon receipt of this letter.

The sale, distribution, and use of this device are restricted to prescription use in accordance with 21 CFR 801.109 within the meaning of section 520(e) of the Federal Food, Drug, and Cosmetic Act (the act) under the authority of section 515(d)(1)(B)(ii) of the act. FDA has also determined that to ensure the safe and effective use of the device that the device is further restricted within the meaning of section 520(e) under the authority of section 515(d)(1)(B)(ii) insofar as the sale, distribution, and use must not violate sections 502(q) and (r) of the act.

Expiration dating for this device has been established and approved at one year. This is to advise you that the protocol you used to establish this expiration dating is considered an approved protocol for the purpose of extending the expiration dating as provided by 21 CFR 814.39(a)(8).

CDRH will publish a notice of its decision to approve your PMA in the FEDERAL REGISTER. The notice will state that a summary of the safety and effectiveness data upon which the approval is based is available to the public upon request. Within 30 days of publication of the notice of approval in the FEDERAL REGISTER, any interested person may seek review of this decision by requesting an opportunity for administrative review, either through a hearing or review by an independent advisory committee, under section 515(g) of the Federal Food, Drug, and Cosmetic Act (the act).

Failure to comply with the conditions of approval invalidates this approval order. Commercial distribution of a device that is not in compliance with these conditions is a violation of the act.

You are reminded that as soon as possible, and before commercial distribution of your device, you must submit an amendment to this PMA submission with copies of all approved labeling in final printed form.

All required documents should be submitted in triplicate, unless otherwise specified, to the address below and should reference the above PMA number to facilitate processing.

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Blvd.
Rockville, Maryland 20850

If you have any questions concerning this approval order, please contact Everette T. Beers, Ph.D. or James F. Saviola, O.D. at (301) 594-1744.

Sincerely yours,

Susan Alpert, Ph.D., M.D.
Director
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure